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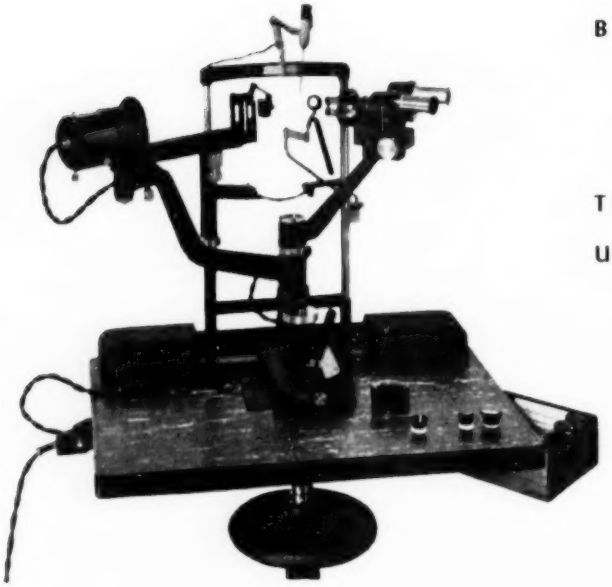

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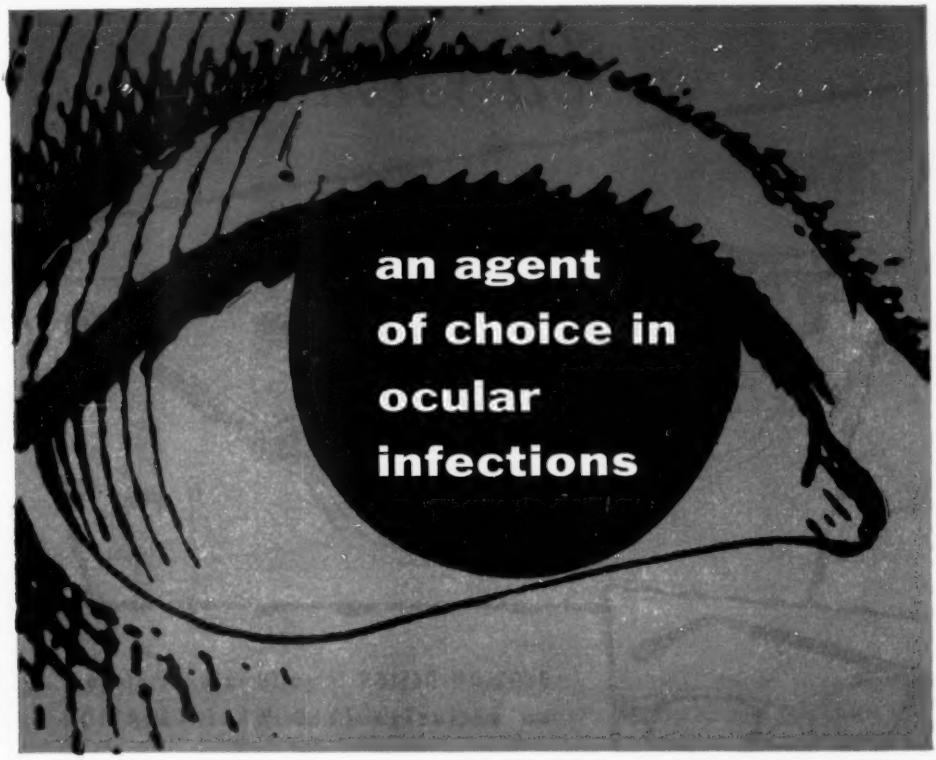

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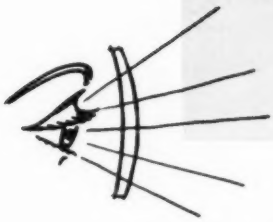

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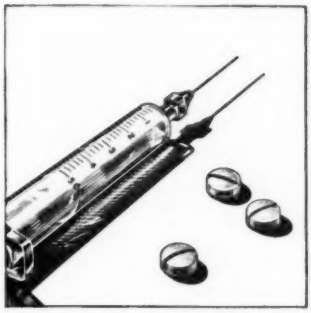

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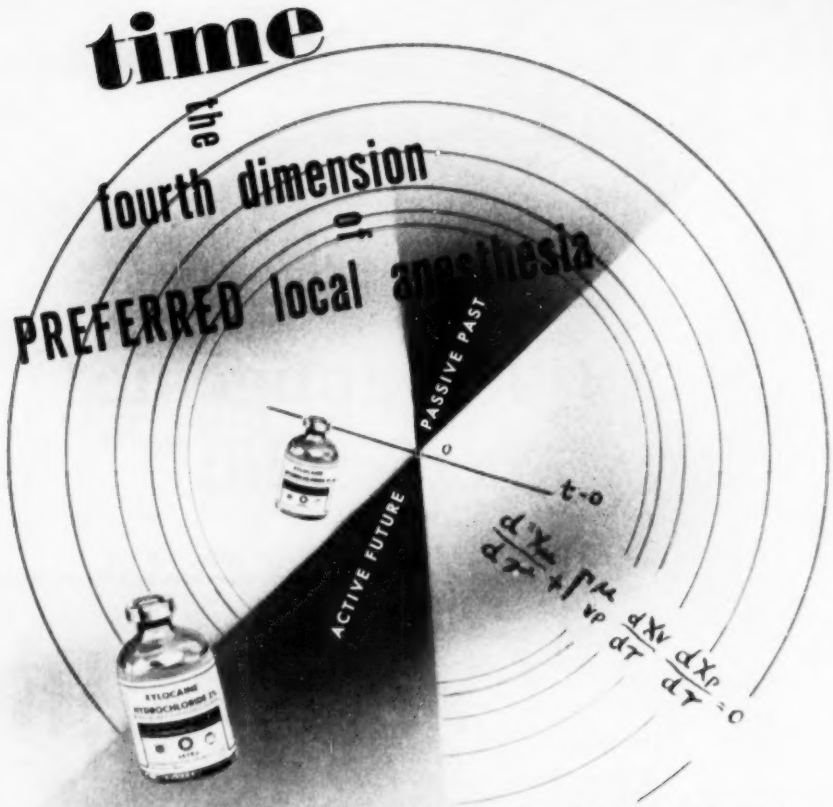

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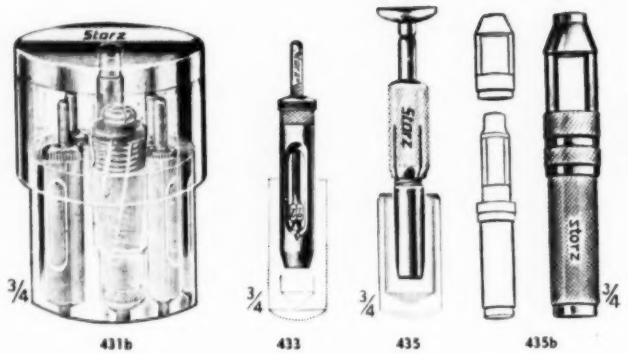

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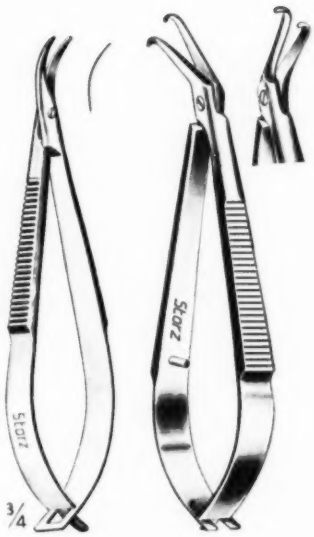

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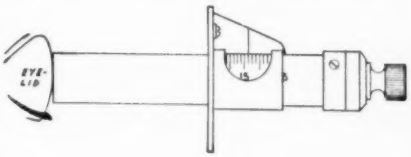

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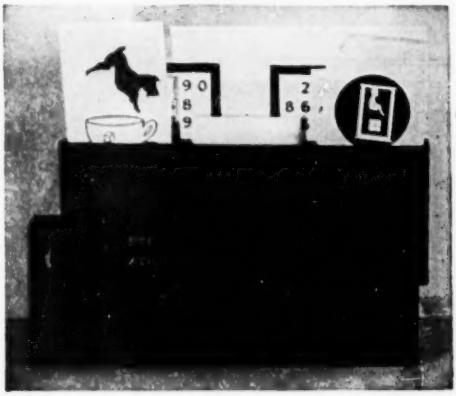

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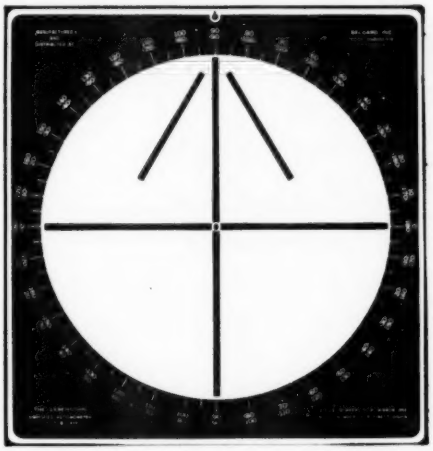

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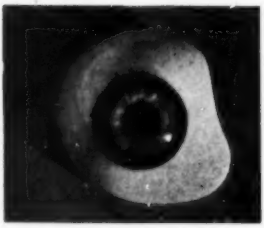

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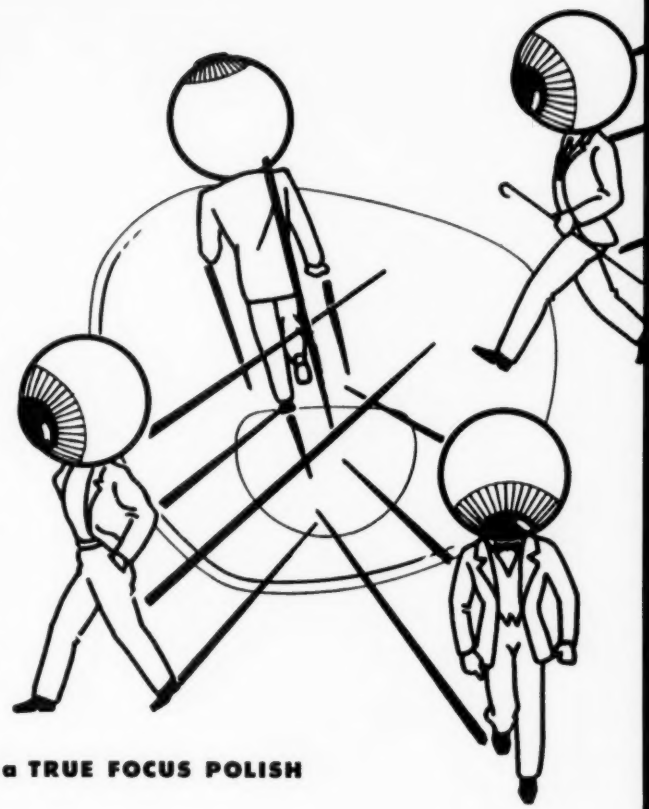

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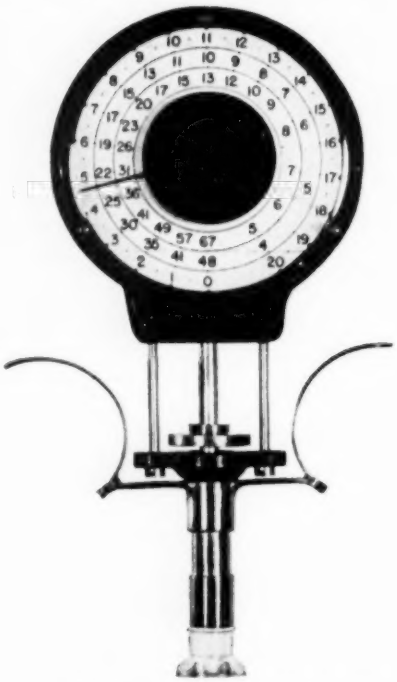

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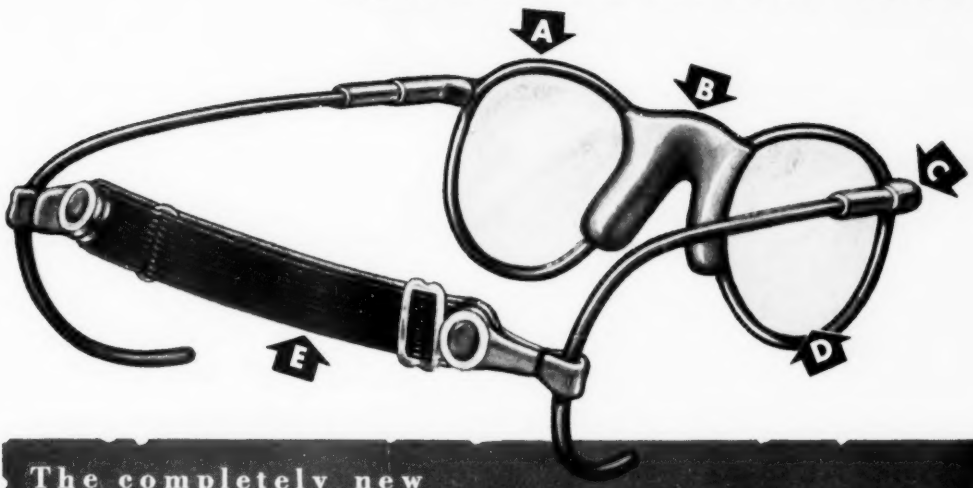

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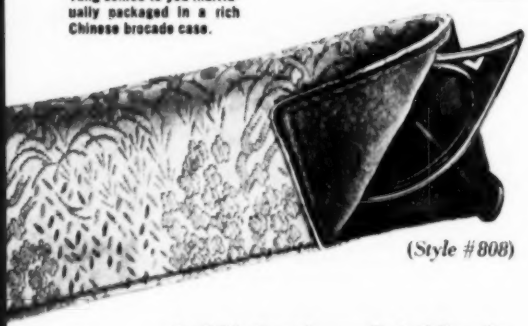

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ABSORBABLE SUTURES IN CATARACT SURGERY

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AND
ELLEN F. REGAN, M.D.
NEW YORK

I CONSIDER it a great privilege to present this lecture because I have long admired Dr. Arthur J. Bedell not only for his ophthalmological achievements but also for his forthrightness. He has demonstrated what can be accomplished if one combines energy and honesty with devotion. We are indeed fortunate that ophthalmology has been his love, for he has greatly enriched our specialty. His photographs of various pathologic conditions of the fundus are known the world over, and American ophthalmology is justly proud of him. Therefore, I welcome this opportunity to salute him.

For many years general surgeons have debated the relative value of absorbable and nonabsorbable sutures, attention being directed primarily to silk and surgical gut (absorbable surgical suture U. S. P.; catgut suture) material. Among the earlier writers, Halsted,[1] in 1913, was strong in his condemnation of surgical gut sutures. This belief in the superiority of silk over surgical gut has been held by others, notably Howes and Harvey,[2] Shambaugh and Dunphy,[3] Gage and Lyons,[4] and Meade and Ochsner.[5] These writers cite the following advantages for silk sutures: 1. They have a greater and more lasting tensile strength. 2. They are more easily sterilized and are manufactured in smaller sizes. 3. They create a limited and predictable tissue reaction. In the face of such statements, it was some time before a strong school favoring the use of surgical gut sutures could arise. Its development was largely the result of studies conducted by Jenkins and his

Presented by Dr. John H. Dunnington as the Bedell Lecture before the Wills Hospital Alumni Society Meeting in Philadelphia, on March 20, 1953.

From the Department of Ophthalmology of Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology of Presbyterian Hospital.

1. Halsted, W. S.: Ligature and Suture Material, J. A. M. A. **60**:1119-1126 (April 12) 1913.

2. Howes, E. L., and Harvey, S. C.: Strength of Wounds Sutured with Catgut and Silk, Internat. J. Med. & Surg. **43**:225-230 (April) 1933.

3. Shambaugh, P., and Dunphy, J. E.: Postoperative Wound Infections and the Use of Silk: An Experimental Study, Surgery **1**:379-385 (March) 1937.

4. Gage, I. M., and Lyons, C.: Symposium on Recent Advances in Surgery: Suture Materials and Their Use, S. Clin. North America **29**:1565-1570 (Oct.) 1949.

5. Meade, W. H., and Ochsner, A.: The Relative Value of Catgut, Silk, Linen, and Cotton as Suture Materials, Surgery **7**:485-514 (April) 1940.

associates [6] on the tissue reactions and tensile strength of these materials, aided in no small measure by the manufacture of finer standardized sterile surgical gut, both chromic and plain. In comparing silk and surgical gut sutures, it is necessary to consider the factors of tissue reaction, tensile strength, and absorbability.

TISSUE REACTION

A. Silk Sutures.—In 1940 Meade and Ochsner [5] pointed out that in the presence of silk sutures so-called dry healing occurs. Studying histologically the tissue reactions around such sutures, they found that during the first two days there was a moderate infiltration of polymorphonuclear leucocytes. This was followed by round-cell, plasma-cell, and fibroblastic proliferation, resulting in encapsulation of the suture strands by the eighth day. At the end of two weeks a thin capsule of fibrous tissue surrounded the silk suture, with little or no cellular reaction.

B. Surgical Gut Sutures.—In contrast, the same authors described the healing around absorbable sutures as "wet healing," characterized by an outpouring of leucocytes and serum, in an attempt to digest the suture material. This reaction they thought tended to delay the proliferation of fibroblasts and subsequent healing. In the case of plain surgical gut they found at the end of 24 hours a pronounced polymorphonuclear-cell and serum response, which increased during the next two or three days. A simultaneous fragmentation of the sutures occurred, but fibroblastic proliferation did not appear until the fifth day. During the next week, as the cellular response became less, the fibroblastic proliferation increased. When chromic surgical gut sutures were employed, an even greater though similar cellular reaction took place over the first 72 hours, but the suture did not fragment. By the fifth postoperative day fibroblasts and round cells were present in the vicinity of the suture, which in this instance remained intact until about the 13th postoperative day. During this time the cellular response subsided, leaving a wide area of fibrous tissue proliferation, which showed some tendency to penetrate the suture plies.

As a result of their studies on tissue reaction about surgical gut sutures, Jenkins and his associates [6c] divided the cellular response into two phases. The first was a leucocytic phase, characterized by invasion of the surgical gut material by polymorphonuclear leucocytes. This occurred with regularity when plain surgical gut was used and in some instances when the suture material had been chromicized. Upon destruction of the surgical gut this cellular response subsided rapidly. The second, or macrophage, stage could be seen between five and seven days after operation and was associated with fibroblastic proliferation. While a sharp transition between the two phases could not be drawn, the findings showed that if polymorphonuclear cell infiltration was severe the invasion of macrophages was not marked and the suture material fragmented and was absorbed more quickly.

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6. Jenkins, H. P., and Hrdina, L. S.: Absorption of Surgical Gut (Catgut): (*a*) I. Decline in Tensile Strength in Tissues, Arch. Surg. **44**:881-895 (May) 1942; (*b*) II. Pepsin Digestion Tests for Evaluation of Duration of Tensile Strength in Tissues, ibid. **44**:984-1003 (June) 1942. (*c*) Jenkins, H. P.; Hrdina, L. S.; Owens, F. M., and Swisher, F. M.: III. Duration in the Tissues After Loss of Tensile Strength, ibid. **45**:74-102 (July) 1942. (*d*) Jenkins, H. P.: IV. Recommendations for Absorbability and Digestibility Specifications, ibid. **45**:323-334 (Aug.) 1942.

TENSILE STRENGTH

As pointed out by Howes,[7] the primary value of sutures is to hold the edges of the wound in apposition for a period of about four days, until healing is sufficiently advanced to prevent wound rupture. He also stated that the immediate strength of a sutured wound depends upon the holding power of the tissues surrounding the suture rather than upon the tensile strength of the suture.[8] Therefore, if the tensile strength of a suture is greater than the holding power of the tissues, the suture is of little value and will tend to cut through the wound edges.

Meade and Ochsner,[5] in their studies on the comparative tensile strength of silk and surgical gut, reported that after knotting, silk has a greater tensile strength than surgical gut, but that silk has the greater tendency to cut through tissue. At the end of four days they found a 30% loss in the tensile strength of chromic surgical gut and a 20% loss in that of silk. After seven days there was a 50% loss in tensile strength of both materials.

Jenkins and associates[6b,c] and Haugaard and associates[9] have studied the decline in the tensile strength of various types of surgical gut sutures. Both groups of workers found that there was nearly always a complete loss in the tensile strength of plain surgical gut in five days. Jenkins and associates[6a,c] also noted that the duration in tensile strength of chromic surgical gut varied with the size of the suture. Chromic surgical gut sutures of smaller sizes retained their tensile strength longer than did the larger sutures, possibly because of the slighter leucocytic reaction produced by them. Haugaard and his co-workers,[9] who processed their own surgical gut, demonstrated that the loss of tensile strength was a little more rapid when very large chromic surgical gut sutures were used. Jenkins and his associates[6] found that there was some variation in the duration of tensile strength in surgical gut sutures supplied by different manufacturers.

ABSORBABILITY

It can be stated that in general the rate of absorption of surgical gut varies with the degree of polymorphonuclear leucocyte response. We have seen that plain surgical gut incites an early tissue reaction; consequently, its rapid absorption is to be expected.[10] Jenkins and associates[6a,c] found it completely absorbed at the end of 10 or 12 days, whereas chromic surgical gut showed a variable rate of absorption. They stated that if a chromic surgical gut suture retains its tensile strength for 10 days, it will take from three to six months to undergo complete absorption. They also pointed out that if a very large chromic surgical gut suture is used, it often will absorb more quickly than a smaller, equally chromicized one, because of the greater foreign body reaction incited by the larger suture.

7. Howes, E. L.: The Strength of Wounds Sutured with Catgut and Silk, Surg., Gynec. & Obst. **57**:309-317 (Sept.) 1933.

8. Howes, E. L.: The Immediate Strength of the Sutured Wound, Surgery **7**:24-31 (Jan.) 1940.

9. Haugaard, G.; Thoennes, L. A., and Hall, M. J.: A Study of the Absorption Characteristics of Surgical Gut, Surg., Gynec. & Obst. **83**:521-529 (Oct.) 1946.

10. Meade and Ochsner.[5] Jenkins and others.[6c]

In spite of Meade and Ochsner's [5] contention that the silk sutures are more satisfactory, Jenkins and associates [6c,d] Howes,[11] and others [12] have stated that in their opinion the objections to surgical gut have been overcome to a large extent. They pointed out that finer surgical gut sutures are now available and that the processes of chromicization and sterilization have been adequately standardized. In their opinion, these improvements have resulted in less tissue reaction and necrosis around the suture and a decreased tendency to infection. Although to date

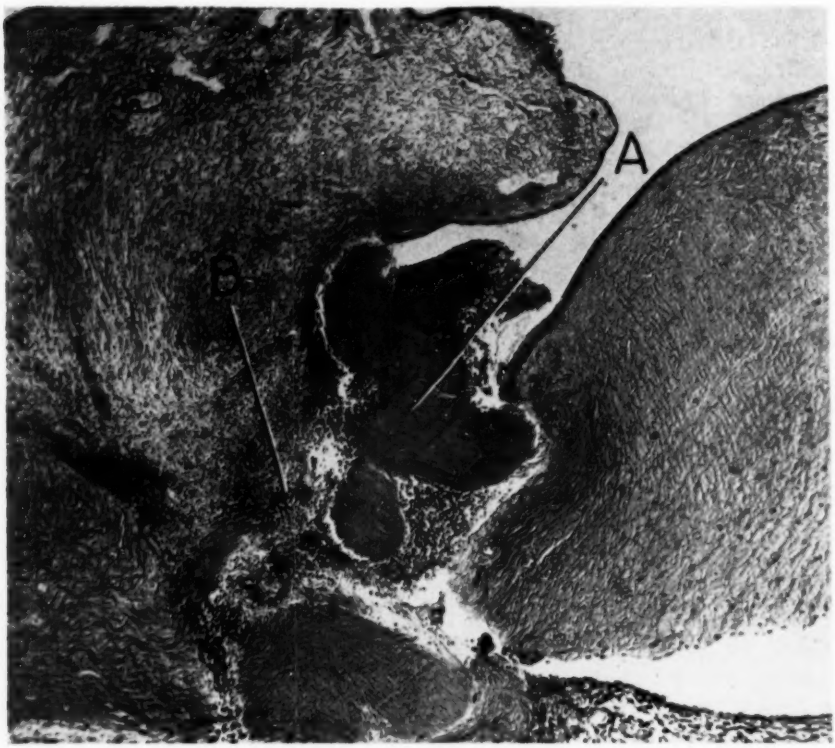

Fig. 1.—Eye of a monkey two days after operation, showing (*A*) intact plain surgical gut suture with (*B*) polymorphonuclear-cell reaction.

there is no agreement on the superiority of absorbable sutures over nonabsorbable (silk) sutures, the ever-increasing use of surgical gut in general surgery is noteworthy.

11. Howes, E. L.: How to Use Catgut, Surg., Gynec. & Obst. **73**:319-323 (Sept.) 1941.

12. Bower, J. O.; Bruns, J. C., and Mengle, H. A.: The Superiority of Very Fine Catgut in Gastrointestinal Surgery, Am. J. Surg. **47**:20-32 (Jan.) 1940. Bower, J. O., and Pearce, A. E.: The Superiority of Fine Catgut over Fine Silk as a Mucosal Suture in Gastric Surgery, Surg., Gynec. & Obst. **74**:649-654 (March) 1942.

OCULAR WOUND HEALING

A. Silk Sutures.—In the course of our histological studies on the healing of cataract incisions, attention was drawn to the reaction occurring around silk sutures used to close corneoscleral incisions, and the following observations were recorded [13]: 1. A downgrowth of epithelium along the suture track. This occurred rapidly, and within two or three days the entire track was often outlined by surface epithelium. 2. Polymorphonuclear-cell infiltration. This was relatively slight during the first week but then increased, until at the end of the third week the

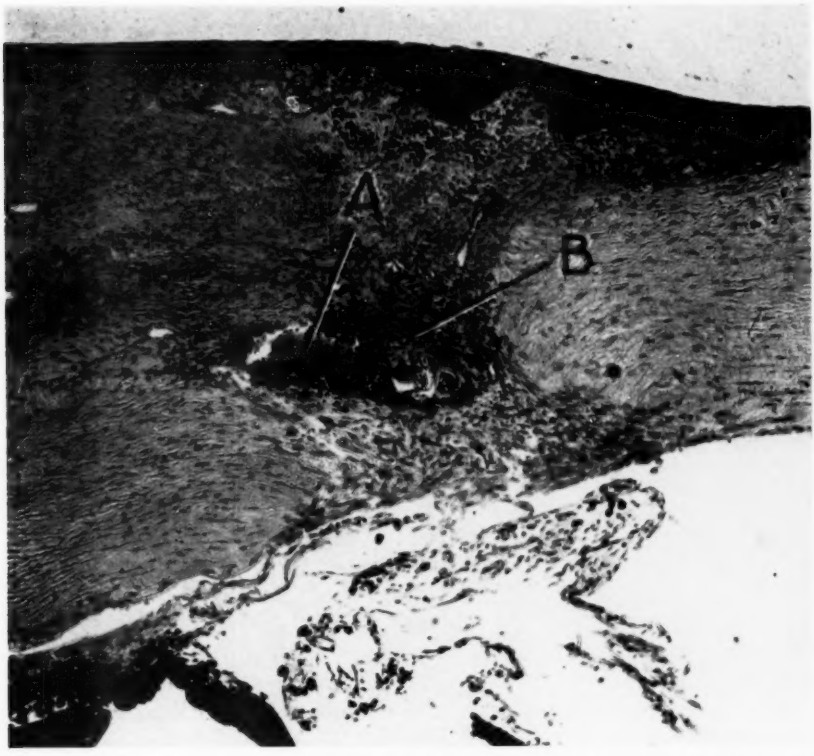

Fig. 2.—Eye of a monkey one week after operation, showing (*A*) fragment of plain surgical gut sutures surrounded by (*B*) round cells and fibroblasts.

suture was usually surrounded by an area of necrosis. By this time, if the suture had been placed properly, it had sloughed out; but if it had been deeply inserted, it remained in place in the midst of necrotic tissue. 3. Fibroblastic proliferation. In the vicinity of the suture this was always decreased, and in the presence of marked necrosis entirely absent. Wounds which otherwise appeared firmly healed at the end of two or three weeks often showed partially healed areas around intact silk sutures.

13. Dunnington, J. H., and Regan, E. F.: The Effect of Sutures and of Thrombin upon Ocular Wound Healing, Tr. Am. Acad. Ophth. **56**:761-772 (Nov.-Dec.) 1951.

These effects of silk sutures upon the healing of ocular incisions prompted us to study the reactions produced by other sutures. Consequently, a series of experiments on the rhesus monkey was conducted, 5-0 plain and 6-0 mildly chromicized surgical gut being used as suture material. The cataract incisions were made with the keratome and scissors and closed with two appositional postsectional corneoscleral sutures. In some instances no conjunctival flap was made; but when such a flap was present, the corneoscleral suture was carried back through the conjunctival flap before being tied. The animals were killed at intervals of 2, 5, 7, 10, 14, 21, and 28 days, and the eyes were sectioned serially.

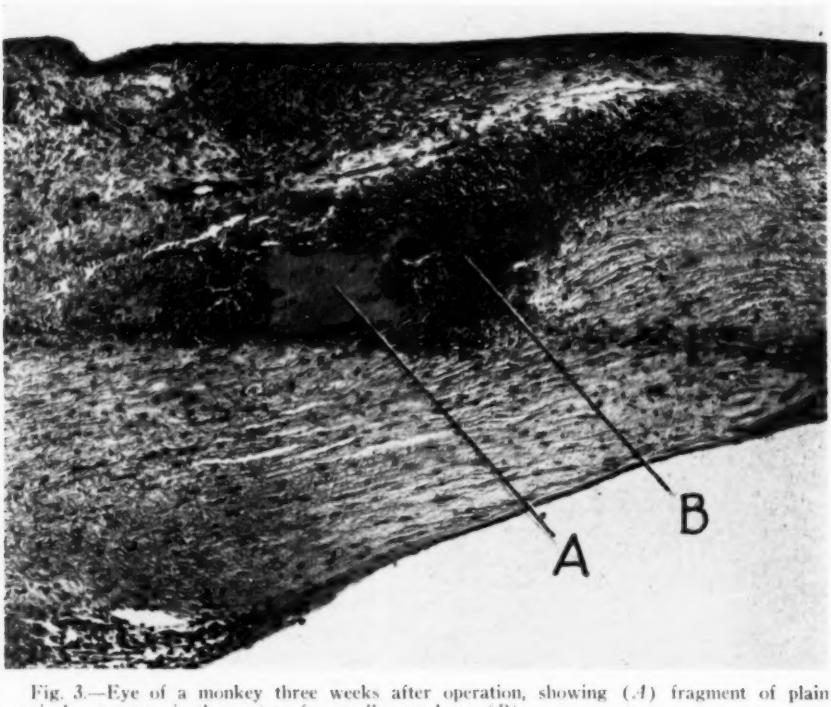

Fig. 3.—Eye of a monkey three weeks after operation, showing (*A*) fragment of plain surgical gut suture in the center of a small granuloma (*B*).

B. Plain Surgical Gut.—In wounds closed with plain surgical gut the initial reaction was a rapid appearance of polymorphonuclear leucocytes around the sutures (Fig. 1). This response was noted at the end of 48 hours. On or about the third postoperative day the suture material began to fragment, and by the sixth day it had undergone marked disintegration. Presumably, as a consequence of the early disintegration of these plain surgical gut sutures, there was little or no tendency to epithelial downgrowth, which was such a striking feature in the wounds sutured with silk. At the end of one week, much of the suture had absorbed, and only fragmented bits could be found. These remnants were surrounded by round cells, both polymorphonuclear leucocytes and macrophages. At this time fibroblastic proliferation was marked and there was no evidence of necro-

sis (Fig. 2). During the second postoperative week the cellular reaction subsided and the polymorphonuclear leucocytes disappeared. Fibroblastic tissue became more prominent, and the wound began to heal firmly. Sometimes small shreds of suture material were seen surrounded by macrophages and occasional giant cells. Such shreds of plain surgical gut that persisted over three weeks became the centers of minute granulomas (Fig. 3). In general, the reaction to plain surgical gut was rapid and of moderate intensity and subsided quickly after fragmentation and absorption of the suture. It is our impression that, although these

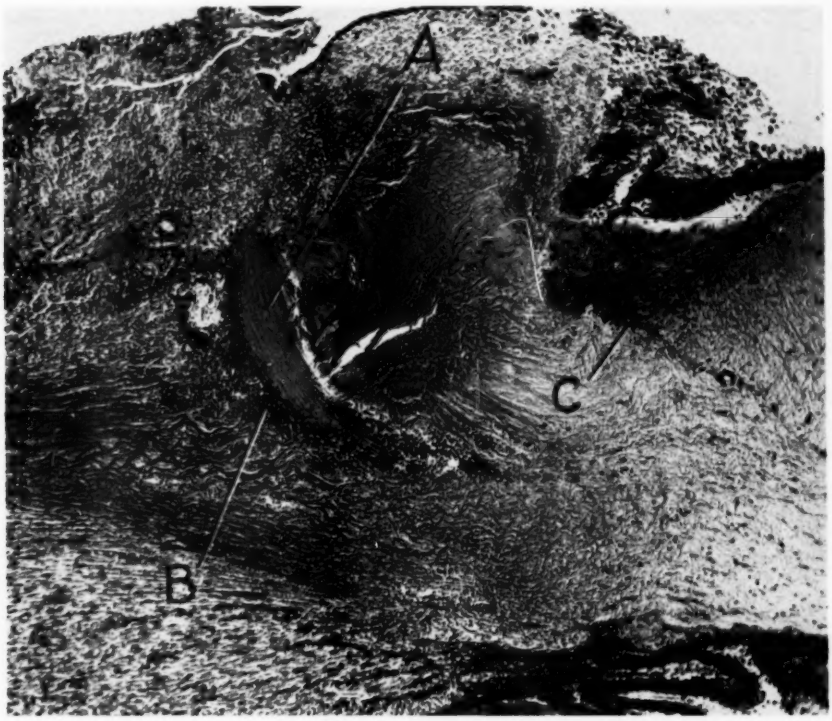

Fig. 4.—Eye of a monkey five days after operation, showing (*A*) intact mildly chromicized surgical gut suture with (*B*) some polymorphonuclear-cell reaction and (*C*) fibroblastic proliferation.

corneoscleral incisions healed well, there was a broader scar of fibrous tissue than was present when silk was used. It is of interest that this was also noticed in general surgical studies by Meade and Ochsner.[5]

C. Mildly Chromicized Surgical Gut.—When 6-0 mildly chromicized surgical gut was used, the initial cellular response was polymorphonuclear in character. This was less marked than that seen with plain surgical gut and occurred largely in the first 72 hours after operation. During this time there was no fragmentation of the suture and healing was evident only in the episcleral tissues. From the fourth to the sixth day, there was little increase in the round-cell infiltration, the suture

tended to remain intact, and fibroblastic proliferation became evident. Epithelial downgrowth and necrosis were minimal (Fig. 4). At the end of the first week there was an increase in the number of round cells, particularly in the macrophages surrounding the suture. At approximately the same time definite fragmentation and absorption of the suture material occurred. In the course of the next week the episcleral vessels became dilated and were more numerous, with definite perivascular cuffing by round cells (Fig. 5). The suture continued to

Fig. 5.—Eye of a monkey two weeks after operation, showing (*A*) knot of chromic surgical gut suture, with (*B*) some round-cell infiltration and (*C*) perivascular cuffing. The wound is firmly healed.

undergo fragmentation and absorption until, by the 21st day, only small bits of it remained, and these were surrounded by macrophages and giant cells. There was no evidence of necrosis, and the process of fibroblastic repair continued unhindered. By the end of the second week the wound was firmly healed. During the third week the cellular reaction disappeared except around suture shreds, which then formed the centers of small granulomas (Fig. 6). Again, the impression was that the fibrous scar was a little broader than that observed with silk sutures.

Thus, the reaction about mildly chromicized surgical gut sutures is characterized initially by a mild polymorphonuclear cell reaction, followed on the sixth or seventh day by a macrophagic response and a fibroblastic proliferation with dilatation of the episcleral vessels. By the 14th day the reaction has largely subsided and the ocular wound appears well healed. At no time is there evidence of definite epithelial downgrowth or necrosis.

Fig. 6.—Eye of a monkey three weeks after operation, showing (*A*) fragment of chromic surgical gut suture as the center of a small granuloma (*B*).

COMMENT

The problem of silk or surgical gut sutures for cataract surgery is by no means solved; but, regardless of the material used, these microscopic studies do indicate certain prerequisites for ideal healing. Both the investigations on wounds sutured with surgical gut and those already reported on the methods of repair with silk have shown that attention to minute details both in the making and in the closing of the incision materially influences the end-results. It is well, therefore, to point out the practical aspects of these histological findings:

Conjunctival Flap.—Most ophthalmic surgeons appreciate the favorable influence of an even conjunctival flap in cataract surgery. Our previous studies have shown that in ocular wounds the initial healing process takes place in the anterior

part of the incision.[14] In the presence of a conjunctival covering there is first a coagulum and then a proliferation of episcleral tissue beneath the flap, whereas without a flap this anterior space is filled with epithelial cells arising from the anterior surface of the cornea. As pointed out by Vail,[15] Theobald and Haas,[16] and others,[17] epithelial invasion of the wound predisposes to epithelization of the anterior chamber. They have shown also that this complication is much less frequent in wounds with an adequate conjunctival flap. Implantation cysts of the anterior chamber have been produced experimentally by incarcerating conjunctival epithelium between the lips of corneoscleral incisions.[18] This original work of Suzaki,[19] which has been confirmed recently by us, emphasizes the need not only of an adequate conjunctival flap but also of careful approximation of its edges.

Section.—It is not our purpose to discuss the relative value of the keratome versus the knife section. The method of making the incision is in our opinion a matter of individual preference. However, it is important for the section to be smooth and for its edges to approximate evenly and without tension. If, as may happen to any surgeon on occasion, an irregularity in the incision occurs, it is our belief that the suture should be placed somewhat away from this site in a smooth, even part of the wound. Our reasoning is that the irregular tongue of tissue already has been subjected to more trauma than the rest of the wound. Consequently, with the added trauma of inserting a suture and the foreign body reaction called forth by the suture material, the amount of necrosis and/or tissue reaction may well be increased to such an extent that proper wound healing will not take place. Howes's[8] precept that the immediate strength of a wound depends on the holding power of the surrounding tissues, and not on the tensile strength of the suture, applies to ophthalmic, as well as to general, surgery. A suture, to be effective, should not be required to draw the edges of the wound into approximation or to hold together jagged lips of the wound. Our histological studies support the contention of Atkinson[20] that it is desirable to bevel the upper part of the incision. If this obliquity extends from 10 to 2 o'clock, the wound surfaces tend to fall into apposition, with little or no gaping. Such wounds require fewer sutures, and the strain placed upon them is reduced to a minimum.

THE SUTURE

A. Material.—Our investigations have shown that the mechanism of wound repair varies with the suture material used. When silk is employed, there is a rapid proliferation of epithelium along the track of the suture. Since this does not

14. Dunnington, J. H.: Healing of Incisions for Cataract Extraction: The Sixth Sanford R. Gifford Memorial Lecture, Am. J. Ophth. **34**:36-45 (Jan.) 1951.

15. Vail, D. T.: Epithelial Downgrowth into the Anterior Chamber Following Cataract Extraction Arrested by Radium Treatment, Tr. Am. Ophth. Soc. **33**:306, 1935; in discussion on Zeiss, E. J.: Posttraumatic Anterior-Chamber Cysts, Am. J. Ophth. **34**:115-120 (Jan.) 1951.

16. Theobald, G. D., and Haas, J. S.: Epithelial Invasion of the Anterior Chamber Following Cataract Extraction, Tr. Am. Acad. Ophth. **52**:470-485 (May-June) 1948.

17. Terry, T. L.; Chisholm, J. F., Jr., and Schonberg, A. L.: Studies on Surface Epithelial Invasion of the Anterior Chamber, Am. J. Ophth. **22**:1083-1110 (Oct.) 1939.

18. Dunnington, J. H., and Regan, E. F.: To be published.

19. Suzaki, A.: Experimental Studies on the Production of Traumatic Serous Iris Cysts, Acta Soc. ophth. jap. (Supp. 34) **10**:1 (Oct.) 1930.

20. Atkinson, W. S.: Preliminary Report of Corneal Section with Long Bevel and Conjunctival Flap for Cataract Extraction, Arch. Ophth. **35**:335 (April) 1946.

occur with surgical gut, one should expect a decreased frequency of epithelial invasion of the anterior chamber in wounds closed with absorbable sutures. The degree of necrosis and round-cell reaction around a mildly chromicized fine surgical gut suture is much less than that around a similar-sized silk one. This undesirable tissue response to silk sutures is especially marked two weeks after their insertion and can be avoided only by removing them on the 9th or 10th day. Plain surgical gut absorbs in two or three days before wound healing is firmly established. Fralick,[21] appreciating the value of a slower-absorbing suture, pioneered in the use of mildly chromicized surgical gut and has long been an advocate of this material. Our investigations show that mildly chromicized surgical gut does not absorb for at least seven days, at which time macrophagic and fibroblastic responses have begun. Accompanying these reactions is a dilatation of the episcleral vessels, which, at least theoretically, should increase the frequency of late anterior-chamber hemorrhages. These enlarged vessels persist for some time and account for the relative slowness with which wounds sutured with this material return to normal. It is our impression that the increased vascularization which occurs in the presence of mildly chromicized surgical gut leads to broader scars and, consequently, a slower stabilization of the refraction.

B. Size.—This is important, for it has been shown that the extent of tissue reaction produced by a suture is proportional to the amount used. It is also true that the greater the reaction the more rapid is the absorption of surgical gut. Moreover, there is no value in having a suture whose tensile strength is greater than that of the surrounding tissue. For these reasons, the smallest possible suture should be used, which in cases of mildly chromicized surgical gut is 6-0 (000000).

Because of recent suggestions that corneoscleral sutures of chromicized surgical gut may well be buried beneath the conjunctival flap, special consideration was given to the reaction about the knot when this material was used.[22] Although the knots were not buried intentionally, in some instances the suture did cut through the conjunctiva and the knot lay half-covered by the conjunctival flap. At these sites there were localized increases in round-cell infiltration, perivascular cuffing, and small granulomas (Fig. 5). These findings are in agreement with those of Jenkins and associates,[6c] who pointed out that the greater the amount of surgical gut embedded in tissues, the greater is the initial foreign body response and the more rapid is the fragmentation of the suture.

C. Number.—These histological studies have shown that any suture material produces an undesirable tissue response. The types of reaction differ with the material used; nevertheless, all suture materials tend to retard healing by encouraging either epithelial invasion and tissue necrosis or increased vascularization. It is, therefore, important to use no more corneoscleral sutures than are necessary to hold the wound surfaces in apposition. In our experience, two such sutures are usually adequate to close the incision if one is placed at 11 o'clock and the other at 1 o'clock and the edges of the conjunctival flap are also sutured.

21. Fralick, F. B.: 6-0 Chromatized Gut in Wound Closure After Cataract Extraction, West Virginia M. J. **46**:251-255 (Sept.) 1950.

22. Roberts, W.: Buried Sutures for Closure of Cataract Incisions, Am. J. Ophth. **35**:1459-1462 (Oct.) 1952.

D. Technique.—Although the size, number, and type of suture materials influence healing, the technique of suturing plays a much more important role. As previously shown, sutures of the mattress type, unless meticulously tied, tend to produce overlapping or gaping of the wound edges.[14] It is felt that the best approximation is achieved with border-by-border sutures firmly, yet not tightly, knotted on the conjunctival surface. Furthermore, this suture should be placed in the superficial third to half of the wound, and the amount of tissue incorporated in the bite should be small. A deep suture tends to foster delayed re-formation of the anterior chamber or its subsequent loss, postoperative hyphema, and, if silk, epithelial downgrowth. If the bite is large, there may be buckling of the wound and/or necrosis of the tissue included within the suture material. The great tensile strength of both the corneal and the scleral fibers makes it possible to secure apposition of the wound surfaces by including only a few of them in the bite. A suture placed in this manner incites a minimal amount of reaction and, at the same time, affords ample protection to the wound.

CONCLUSIONS

Histological studies have been made on corneoscleral wounds sutured with plain and mildly chromicized surgical gut in order that the tissue responses to these materials might be compared with those found in wounds closed with silk. It had been shown that in the presence of silk, tissue necrosis and epithelial ingrowth along the track of the suture were the outstanding reactions. Neither of these responses was noted when absorbable sutures were employed. The initial response with surgical gut was found to be a polymorphonuclear-cell reaction, which with the plain type was rapid and marked, leading to an early disintegration of the suture. When mildly chromicized material was used, this polymorphonuclear-cell response was less pronounced, and the suture remained intact for about seven days. Fibroblastic proliferation became evident about the fifth day, as did increased vascularization of the wound. During the next week the healing process progressed, and at the end of 14 days the wounds appeared well healed but somewhat broader and more vascularized than a comparable one closed with silk. The increased vascularization of these wounds is an undesirable feature, but this feature is counterbalanced by the relative absence of tissue necrosis and of epithelial invasion. In view of these findings and our present clinical experience, we believe that mildly chromicized surgical gut is a satisfactory material for closing cataract incisions.

CLINICAL AQUEOUS OUTFLOW

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IN RECENT years considerable knowledge has been added to our understanding of aqueous outflow. Although it had been known for many years that patients with chronic simple glaucoma had a decreased facility (increased resistance) of aqueous outflow,[1] it is through the recent efforts of Goldmann[2] and Grant[3] that these findings have been placed on a more quantitative basis. The facility of outflow is a coefficient representing the outflow in cubic millimeters per minute per millimeter of mercury pressure gradient. It is, therefore, a measure of the ease with which aqueous can leave the eye. Goldmann determined aqueous outflow and facility of outflow in the undisturbed eye by measuring the turnover rate of fluorescein in the anterior chamber (K_F),[4] the volume of the anterior chamber (V_A), and the difference between intraocular pressure (P_O) and episcleral venous pressure (P_V). Grant has calculated the facility of outflow from a continuous tracing of the fall in intraocular pressure produced by a tonometer on the eye. Using such entirely independent methods of measurement, Grant and Goldmann have obtained comparable values for the average normal coefficient of facility of outflow (C) (Grant,[3] 0.22; Goldmann,[2] 0.33) and remarkably similar values for normal aqueous outflow (Grant, 2.4 cu. mm. per minute; Goldmann, 2.2 cu. mm. per minute). The agreement of the average normal values obtained by such diverse methods lends credence to the correctness of the theoretical and mathematical interpretation, as well as to the accuracy of the measurements used by both these investigators. Although both methods have obvious sources of error, these may be inconsequential or partially

This work was supported by a grant from the Kellogg Foundation of Michigan and was carried out at the Wilmer Ophthalmological Institute of The Johns Hopkins Hospital.

1. Knies, M.: Über das Glaucom, Arch. Ophth. **22**:163, 1876. Schoenberg, M. J.: Clinical and Experimental Researches on Intra-Ocular Drainage: Preliminary Report, Arch. Ophth. **42**:117, 1913.

2. Goldmann, H.: Zur Frage des Sitzes der Widerstandserhöhung beim einfachen Glaukom, Ophthalmologica **119**:267, 1950; Das Minutenvolumen der menschlichen Vorderkammer bei Normalen und bei Fällen von primärem Glaukom, ibid. **120**:150, 1950; Über die Wirkungsweise der Cyclodialyse, ibid. **121**:94, 1951; Die Wirkungsweise der Iridektomie beim chronisch kongestiven Glaukom, ibid. **123**:202, 1952; Abflussdruck, Minutenvolumen und Widerstand der Kammerwasserströmung des Menschen, Docum. ophth. **5**:278, 1951.

3. Grant, W. M.: (*a*) Tonographic Method for Measuring the Facility and Rate of Aqueous Flow in Human Eyes, Arch. Ophth. **44**:204, 1950; (*b*) Clinical Measurements of Aqueous Outflow, ibid. **461**:113, 1951.

4. The symbols used in this paper are not always those of the authors cited, but are converted to a single consistent system for purposes of comparison.

cancel one another in the normal eye. Determinations on the same eye by the two methods would be of the greatest importance. The enormous variations of facility of outflow observed in normal subjects, especially by tonography, suggested an investigation of possible sources of error. Furthermore, when one explores certain pathologic conditions of the eye, one must be aware of the additional possible errors inherent in each method. Although the over-all agreement and similarity of most conclusions drawn prevail in abnormal eyes, the variations become more evident. Corrections for such errors as can be evaluated might narrow the limits of normal and delineate more sharply the glaucoma group, thus making the measurements more useful clinically.

I. METHODS OF MEASUREMENT AND SOURCES OF ERROR

A. Goldmann's Method.—In order that the methods of measurement of the facility of aqueous outflow and the errors involved may be better understood, it is helpful to consider the following equations (modified from Goldmann):

(1) Outflow pressure gradient × facility of outflow = outflow, in cubic millimeters per minute

$$(P_o\text{-}P_v) \times C_o = F$$

(2) Facility of outflow = outflow per minute/outflow pressure gradient

$$C_o = \frac{F}{(P_o - P_v)}$$

where C_o = facility of outflow in the undisturbed eye; F, outflow, in cubic millimeters per minute; P_o, intraocular pressure, and P_v, episcleral venous pressure in the undisturbed eye.

Goldmann has calculated the outflow of aqueous (F) by determination of the turnover rate of fluorescein in the anterior chamber after intravenous injection. The outflow of fluorescein, in percentage per minute (K_F), multiplied by the volume of the anterior chamber, in cubic millimeters (V_A), gives a value of outflow (F) in cubic millimeters per minute.

$$(3)\ F = \frac{K_F \times V_A}{100}$$

where K_F equals turnover rate coefficient of fluorescein in anterior chamber (percentage per minute), and V_A, volume of anterior chamber, in cubic millimeters.

From Equation 2, Goldmann was then able to calculate a value for C_o, the facility of outflow. It soon became apparent that this was the most significant value in glaucomatous eyes. It was on the basis of the marked depression of facility of outflow in glaucoma that Goldmann concluded that obstruction between the anterior chamber and the episcleral veins was the mechanism of the elevation of pressure in this disease.

The method of Goldmann has the enormous advantage that one is working on an undisturbed eye. However, the most significant clinical value, the facility of outflow (C_o) is determined more indirectly by this method and is, therefore, subject to the summation of errors involved in the measurement of turnover of fluorescein, volume of anterior chamber, episcleral venous pressure, and intraocular pressure. Caution must be exercised in order to rule out spontaneous changes in intraocular pressure (P_o) during the measurement of turnover of fluorescein. Furthermore, the conversion of turnover rate data to outflow values requires information as to the role of diffusion in the influx and outflow of fluorescein in the normal eye. The approxi-

mations made necessary because of the lack of this information may prove to be a sizable source of error. Disregard of diffusion of fluorescein will lead to an overestimation of outflow and, therefore, of facility of outflow in the normal eye. In addition, any variation in the permeability of the blood-aqueous barrier to fluorescein will lead to completely abnormal turnover values, and thus to abnormal values for flow and facility. Increased permeability to fluorescein will be interpreted as increased flow by this method. Thus, one must be very cautious in interpreting values in the early postoperative period, in uveitis, and in acute congestive glaucoma. Although the method can be used to determine flow in eyes with filtering blebs, these values cannot be converted to facility of outflow because no reasonable estimate can be made of the outflow pressure. Finally, it should be noted that this method requires more elaborate apparatus, is much more difficult and time-consuming to perform, and is thus not practical as a routine clinical procedure.

B. Method of Grant.—Tonography as described by Grant, on the other hand, is simple and practical to carry out. Most important, it affords a much more direct measure of facility of outflow. It has the major objection that measurements are made under the unphysiological conditions imposed by a tonometer on the eye. As pointed out below, there is reason to believe that Grant's method of calculation leads to an underestimation of facility of outflow. Although the method has already proved itself most valuable in several clinics, there is considerable variation among normal eyes, and there is a most disturbing overlap of values for normal and abnormal eyes. A more detailed outline of the errors involved in tonography might reveal sources of this wide scatter of results.

In tonography, a tonometer is placed upon the eye for four or five minutes, and a continuous tracing of the tonometric scale reading is recorded. The general equation for the changes taking place in the eye under these conditions may be written as follows:

$$(4)\quad C_t = \text{outflow per minute/outflow pressure gradient}$$

$$C_t = \frac{\Delta V_S + \Delta V_C + \Delta V_B + FT}{T} \Big/ (P_{tav} - P_{Vt})$$

where F equals rate of aqueous inflow and outflow (cubic millimeters per minute) in the undisturbed eye; T, time in minutes; ΔV_S, change in scleral distention during tonography; ΔV_C, change in corneal indentation during tonography; ΔV_B, change in volume of blood in the eye during tonography; P_{tav}, average pressure in the eye during tonography (with tonometer on the eye); P_{Vt} episcleral venous pressure with tonometer on the eye, and C_t facility of aqueous outflow in the eye with tonometer in place.

If one makes the following assumptions: (*a*) There is no change in rate of secretion and diffusion of aqueous during tonography (i. e., F is constant and the same as in the undisturbed eye); (*b*) there is no change in volume of blood in the eye during tonography (i. e., $\Delta V_B = 0$); (*c*) episcleral venous pressure during tonography is the same as in the undisturbed eye (i. e., $P_{Vt} = P_V$), and (*d*) facility of aqueous outflow with a tonometer on the eye is the same as that in the undisturbed eye (i. e., $C_t = C_o$)

then Equation 4 reduces to the equation Grant has used:

$$(5)\quad C_T = C_o = \frac{\Delta V}{T} \Big/ (P_{tav} - P_o)$$

where $\Delta V = \Delta V_C + \Delta V_S$.

From Friedenwald's data,[5] values for corneal indentation (V'_c) and scleral distention (V_s) are available for all tonometric scale readings, as are values for P_t and P_o.

If average values for radius of corneal curvature and coefficient of scleral rigidity are assumed, the equation for the change in volume may be written:

$$(6)\ \triangle V = \triangle V_c + \triangle V_s = \left[V_{c_2} - V_{c_1}\right] + \left[1/K_s \times \log \frac{P_{t_1}}{P_{t_2}}\right]$$

where K_s equals average coefficient of scleral rigidity; P_t, intraocular pressure with tonometer on the eye, and V_c, corneal indentation by tonometer for average radius of corneal curvature.

Tables may be set up for values of V for all plunger readings where

$$(7)\ V = V_c - 1/K_s \times \log P_t$$

From such tables ΔV may be determined by simple subtraction. For determination of flow (F) through the eye from tonographic results, Equation 1 may be used, i. e., $F = (P_o - P_v) \times C_o$. Grant at first disregarded P_v but later set it equal to 4 mm. Hg. Goldmann gives an average value of 10 mm. Hg for normal episcleral venous pressure. This difference in calculation would more than account for the slightly higher values for aqueous outflow reported by Grant.

Let us now go back over the various assumptions made in the derivation of Equations 5 and 6 of Grant from the more general Equation 4 in order to evaluate possible sources of errors in utilizing the simplified equation.

1. Is there no change in rate of flow of aqueous during tonography; i. e., is F constant?

The conclusion that there is no change in rate of flow of aqueous during tonography assumes that the tonometer remaining on the eye does not in any way, mechanical or reflex, affect secretory or diffusion mechanisms. In the average normal eye the changes in corneal indentation ($\Delta V'_c$) and scleral distention ($\Delta V'_s$) during tonography each amount to about 5 cu. mm. Since approximately 10 cu. mm. of aqueous passes through the undisturbed normal eye in an interval corresponding to that required for tonographic determination, small changes in this value will cause large errors in the determination of $\Delta V'$. A decrease in F would lead to an overestimation of $\Delta V'$ and C; an increase in F would be recorded as an underestimation of $\Delta V'$ and C. There are very few experimental data available on the effect of tonography on secretion and diffusion, but it would appear to be a most important factor to be established. Preliminary studies on the effect of tonography in rabbits should be mentioned. If one injects 200 mg. of ascorbic acid intravenously into normal rabbits and measures the concentration of ascorbic acid in the posterior chamber, one finds it to rise over 100% in 10 minutes. This rise in ascorbic acid concentration appears to be markedly inhibited in the eye to which a tonometer has been applied for the 10-minute interval.

It is of interest to note that if Grant's value for C_o is used and outflow (F) is calculated by Equation 1, extremely low values for F are obtained. This may be due to an underestimation of C_o or a decrease in through flow (F) due to the tonometer on the eye. Grant has avoided this difficulty by assuming a much lower value

5. Friedenwald, J. S.: Some Problems in the Calibration of Tonometers, Tr. Am. Ophth. Soc. **45**:355, 1947.

(4 mm. Hg) for episcleral venous pressure than that measured by Goldmann (average, 10 mm. Hg for normal eyes; 8 mm. Hg for glaucomatous eyes). This may indicate that the close agreement in normal values for F by the two methods is more apparent than real. It may also explain some of the discrepancies noted in diseased eyes. Many more observations and other experimental approaches are needed to determine the magnitude and significance of the effects of tonography on secretion and diffusion of aqueous in normal, and especially in glaucomatous, eyes. Only then can this source of error be ignored or the correction applied.

2. Does the volume of blood in the eye remain constant during tonography? (Is $\Delta V_B = 0$?)

The volume of blood in the normal eye is over 200 cu. mm. Small changes in this volume during tonography will obviously induce errors in the calculations of sizable magnitude. It is well known that vasodilatation will influence intraocular pressure. Thus, Kochmann and Römer [6] in 1914, in animals, and Baillart and Bollack [7] in 1921, in men, observed considerable increases in intraocular pressure following inhalation of amyl nitrite. Similarly, amyl nitrite or blushing will induce sudden conspicuous rises in the tonographic tracing. The effects of changes in blood pressure in the opthalmic artery on intraocular pressure have been repeatedly described. Variations in blood pressure with changes in pulse and respiration are faithfully transmitted as changes in intraocular pressure (Duke-Elder and associates [8]). As early as 1866,[9] carotid compression was known to produce a fall in intraocular pressure in the homolateral eye. Bárány [10] has recorded homolateral falls of 30 to 40 mm. Hg in the ophthalmic artery and of 4 mm. Hg in the intraocular pressure of rabbits following unilateral carotid occlusion. If the homolateral carotid artery is compressed during tonography, there is a precipitous fall in the intraocular pressure tracing. Furthermore, Adler and associates,[11] in 1924, noted that a ligature around the aorta of cats produced a rise in blood pressure of approximately 74 mm. Hg and a rise in intraocular pressure of about 7 mm. Hg. The rise in intraocular pressure induced by increasing orbital venous pressure or by placing a ligature around the neck was described by Wessely,[12] in 1908. It is clear that the blood volume factor and, particularly, the effects of blood pressure variations on tonography, can be very important sources of error. Variations in blood pressure may be

6. Kochmann, M., and Römer, P.: Experimentelle Beiträge zum pathologischen Flüssigkeitswechsel des Auges, Arch. Ophth. **88**:528, 1914.

7. Baillart, P., and Bollack, J.: De l'action comparée de certaines substances médicamenteuses sur la tension intra-oculaire et sur la pression artérielle, Ann. ocul. **158**:641, 1921.

8. Colle, J.; Duke-Elder, P. M., and Duke-Elder, W. S.: Studies on the Intra-Ocular Pressure: Action of Drugs on Vascular and Muscular Factors Controlling Intra-Ocular Pressure, J. Physiol. **71**:1, 1931.

9. Adamük, E.: Manometrische Bestimmungen des intraocularen Druckes, Centralbl. med. Wissensch. **41**:561, 1866.

10. Bárány, E. H.: The Influence of Intra-Ocular Pressure on the Rate of Drainage of Aqueous Humour, Brit. J. Ophth. **31**:160, 1947.

11. Adler, F. H.; Landis, E. M., and Jackson, C. L.: Tonic Effect of Sympathetic on Ocular Blood Vessels, Arch. Ophth. **53**:239, 1924.

12. Wessely, K.: Experimentelle Untersuchungen über den Augendruck, sowie über qualitative und quantitative Beeinflussung des intraokularen Flüssigkeitswechsels, Arch. Augenh. **60**:97, 1908.

spontaneous or induced by the subject's lying flat, by noises, by emotional or other stimuli, or by oculocardiac or other reflex changes produced by the tonometer on the eye. In addition, the direct effect of the pressure of the tonometer in expelling blood from the eye has not been ruled out and may vary from patient to patient, depending upon the rigidity of the vascular bed. Vascular rigidity is a factor in the scleral rigidity coefficient (K_S). Variations from the average normal coefficient of scleral rigidity assumed by Grant may thus influence the calculations greatly in the individual case.

3. Is episcleral venous pressure (P_V) during tonography the same as that in the undisturbed eye?

To our knowledge, no measurements are available on the effects of tonography on episcleral venous pressure. It would seem unlikely that episcleral venous pressure would not be influenced by the weight placed on the globe and the compression against the rigid orbit. The tonometer with the 5.5-gm. load weighs approximately 16 gm. This load is supported by the eyeball, and hence by the orbit. If it is assumed that the cornea-sclera-anterior orbital fascia-orbital walls complex makes a watertight chamber, then the load (16 gm.) is distributed over the area of the circle of insertion of the anterior orbital fascia into the sclera.[13] This circle is roughly 1.5 cm. in diameter, or 1.7 sq. cm. in area. Therefore, 16 gm. per 1.7 sq. cm., or about 10 gm. per square centimeter, or 7 mm. Hg, is the approximate intraorbital pressure required to float the tonometer. If the pressure in the orbital veins is less than this, tonometry will cause orbital stasis and increased episcleral venous pressure. The corresponding pressure for the 10-gm. weight would be approximately 9 mm. Hg. It should also be noted that the fluid forced out of the globe by the tonometer may also independently raise episcleral venous pressure. It is hoped that direct measurements of the effects of tonography on episcleral venous pressure will be accomplished in the near future.

4. Is the facility of outflow in the eye at the higher pressures induced by tonography the same as that in the undisturbed eye?

Determination of the validity of this assumption will require the use of Goldmann's and Grant's methods on the same patient under the same conditions. Such measurements would be most useful in establishing the validity of the values obtained by tonography. It should be noted that Goldmann's data reveal an average normal facility of outflow of 0.33 in the undisturbed eye, with variations of normal from 0.23 to 0.66, whereas Grant has reported an average normal of 0.22 for the eye with the tonometer in place, with variations of normal from 0.11 to 0.44. The lower values may be accounted for by the effect of the tonometer on various factors, such as secretion, episcleral venous pressure, and diffusion, or on the facility itself. It is also possible that some systematic error in Goldmann's method, such as overestimation of episcleral venous pressure, yields false high values for facility with this method.

Furthermore, the differences in facility of outflow determined with different weights in some eyes strongly suggest an effect of the tonometer on the facility coefficient. Thus, as indicated above, the average normal facility of outflow with a 5.5-gm. weight is about two-thirds that computed from Goldmann's data. Kron-

13. Friedenwald, J. S., in discussion on Grant, [3b] p. 124.

feld [14] has noted that in some eyes measurement with a 10-gm. weight results in a lower coefficient facility than with a 5.5-gm. weight on the same eye. These observations would indicate that facility of outflow is not independent of the load on the eye and the pressure in the eye.

5. Do variations from average values for corneal curvature and scleral rigidity affect tonography?

It has been pointed out by Friedenwald [13] that Grant's Equation 6 and Equation 7 assume average values for K_s, the coefficient of scleral rigidity, and V'_c, the volume of indentation of the cornea by the tonometer. More precise values for these factors can be determined and used for the individual patient. The coefficient of scleral rigidity can be measured, as described by Friedenwald, by tonometric measurements with two different weights. Corneal curvature can be precisely measured by a keratometer and a suitable correction factor applied to V'_c.

C. Present Study.—The work in the tonographic laboratory of the Wilmer Ophthalmological Institute has been limited to the application and modification of Grant's

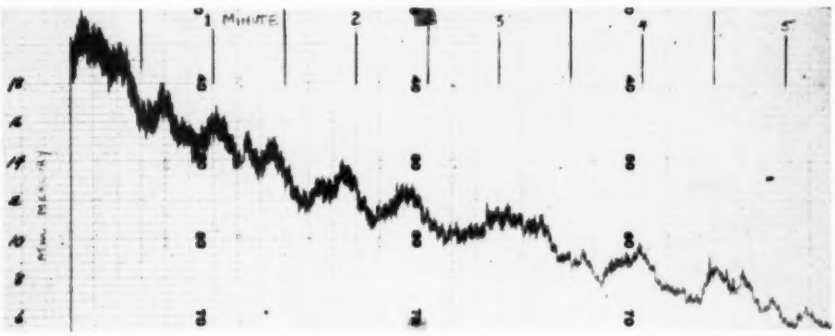

Fig. 1.—Tonographic tracing of normal eye. Scale at left represents intraocular pressure, P_o, in millimeters of mercury.

method of tonography. Efforts have been made to determine the value and limitations of the method. Particular attention has been paid to the detection, evaluation, and correction of sources of error. Fortunately, a very accurate recording system was secured by connecting the electronic tonometer to a Brown potentiometer. This provided six times the amplification afforded by Grant's original method (Fig. 1). This permitted observation on the tracings of the variations of intraocular pressure with pulse and respiration. Superimposed on these more rapid oscillations, the plateau effects described by Kronfeld,[14] as well as definite larger and slower wave-like variations in intraocular pressure, at the rate of three to six per minute, were noted early in the study. As described above, large variations in intraocular pressure can be induced by variations in blood pressure or ocular vasodilation. It seemed possible, therefore, that these slow waves might be related to the Traube-Hering blood pressure waves. In some subjects they were synchronous with phasic variations in the size of the pupil but persisted after cycloplegia.

In exploration of the relation of these waves and other irregularities in the tracings to variations in blood pressure, a continuous blood pressure recording would

14. Kronfeld, P. C.: Tonography, A. M. A. Arch. Ophth. **48**:393, 1952.

be necessary. By this means, simultaneous tracings of blood pressure and intraocular pressure might be recorded. This would provide a means of estimating the effects of changes in blood pressure, reflex, accidental, or spontaneous, on the tonographic tracing. Although no satisfactory practical method could be found for continuous blood pressure recording in patients, the Lange[15] apparatus has been acquired recently. This affords an automatic intermittent recording of either diastolic or systolic blood pressure, which can be run simultaneously with tonography. It became evident at once that the slow waves noted in the ocular tracings were synchronous with phasic variations in the diastolic blood pressure. Furthermore, it was noted in some patients that the application of the tonometer, or even the turning on of the recording machine, was associated with a steep rise in diastolic blood pressure. In these instances the tonographic tracing showed a considerably greater fall in

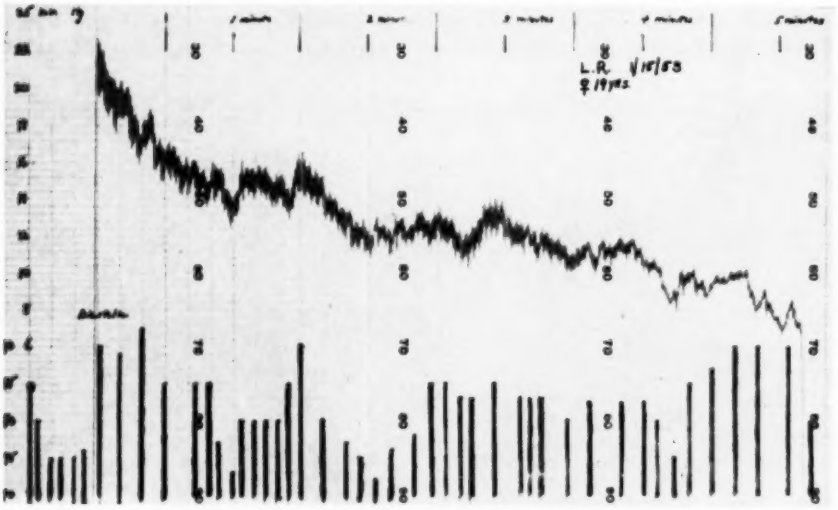

Fig. 2.—Simultaneous tonographic and diastolic blood pressure tracings. Scale at left represents brachial diastolic pressure, below, and intraocular pressure, above, in millimeters of mercury.

the first minute than in subsequent parts of the curve, and these correlated well with blood pressure changes (Fig. 2). Such initial blood pressure spikes will give false high readings for P_0 and $\Delta I'$ and markedly affect the value calculated for facility of outflow. They are of sufficient magnitude to give false-normal results in glaucomatous eyes. Although the correlation of these blood pressure effects has been just begun, it is quite apparent that variations in blood pressure do occur and are capable of influencing intraocular pressure. It is also evident that the arbitrary choice of the initial tonographic reading and a point four or five minutes later may be an unfortunate one in many instances. One must choose two points on the tonographic tracing where the blood pressure had the same value and extrapolate back to zero time

15. Lange, K.: A Recording Sphygmotonograph: A Machine for the Continuous Recording of Systolic and Diastolic Arterial Pressure in Man, Ann. Int. Med. **18**:367, 1943.

in order to avoid or minimize this large source of error. It is planned to apply this observation to a series of patients in the near future in an attempt to evaluate how much the boundaries of the normal and the abnormal may be separated.

In addition, calculations have been carried out for the variations in volume of corneal indentation (V_c) with deviations from average corneal curvature. Scleral rigidity determinations, as well as keratometer readings, have been made on most of the patients studied. It may be concluded that it is only in those patients exhibiting marked deviations from the normal values for corneal curvature that this factor will induce more than a 10% error in the determination of facility of outflow. The error introduced by the deviation from the average normal value for scleral rigidity is considerably larger. From Friedenwald's curves for the frequency distribution of ocular rigidity, it is evident that about 1 eye in 20 will have greater than a 30 to 50% error in K_8 or a 15 to 25% error in ΔV. Since the values for P_0 will also vary with K_8, the possible error in calculation of facility (C) can be as much as 50% in some eyes.

It is planned to investigate in detail some of the above-described sources of error in tonography. These will be the subject of future reports from this laboratory.

II. CLINICAL APPLICATION OF TONOGRAPHY

In spite of the errors involved in the calculations and the difficulties in theoretical interpretation, tonography has proved of great aid in diagnosis and evaluation of therapy of glaucoma. It has also proved of value in the exploration of the physiological variations of intraocular pressure and the mechanisms of the actions of certain drugs and surgical procedures, and in the refinement and evaluation of provocative tests. The results recorded below are based on reports in the literature,[16] as well as an analysis of over 1,500 tracings on more than 250 patients seen in the tonography laboratory of the Wilmer Ophthalmological Institute.

A. Diagnosis of Glaucoma.—1. Untreated Open-Angle Glaucoma: The findings of Grant and others were readily verified. There was a marked decrease in facility of outflow in almost all cases of untreated open-angle glaucoma (Fig. 3*A*). The facility coefficient, as measured by Grant's formula, was usually between 0 and 0.10 for these patients, as compared with 0.15 to 0.55 for normal subjects. Unfortunately, there was a sizable overlap of coefficients for glaucomatous and normal eyes between the values of 0.10 and 0.15, and a few untreated glaucoma patients had occasional tracings with coefficients above 0.15, but such cases were exceedingly rare and may be explained on the basis of initial changes in blood pressure. With the use of Goldmann's method, a similar decrease of facility has been reported. With both methods

16. (*a*) Grant.[3] (*b*) Kronfeld.[14] (*c*) deRoetth, A., Jr., and Knighton, W. S.: Clinical Evaluation of the Aqueous-Flow Test: Preliminary Report, A. M. A. Arch. Ophth. **48**:148, 1952. (*d*) Prijot, E., and Weekers, R.: Mesure de la résistance à l'écoulement de l'humeur aqueuse au moyen du tonomètre électronique: 1re partie: Résultats chez le sujet normal, Ophthalmologica **123**:1, 1952. (*e*) Weekers, R., and Prijot, E.: 2e partie: Résultats chez les sujets atteints de glaucome chronique non inflammatoire, ibid. **123**:114, 1952; (*f*) 3e partie: Résultats chez les sujets glaucomateux opérés par la diathermie rétrociliaire thermométrique, ibid. **123**:365, 1952. (*g*) Prijot, E., and Weekers, R.: 4e partie: Mode d'action de la pilocarpine dans le glaucome chronique non inflammatoire, ibid. **124**:12, 1952. (*h*) Weekers, R., and Prijot, E.: 5e partie: Mode d'action de l'iridencleisis dans le glaucome chronique non inflammatoire, ibid. **124**:166, 1952.

the total aqueous outflow per minute was normal, or somewhat reduced. In this disease process, therefore, there is a markedly elevated outflow pressure, and an even more striking decrease in facility of outflow, with a resulting small decrease in fluid flowing through the eye.

In our experience, many patients with so-called low-tension glaucoma have a constantly decreased facility of outflow even at the normal levels of intraocular pressure they maintain (Fig. 3*B*). Tonography has provided an almost unique method for suggesting the diagnosis of this disease, and this constitutes one of its major uses. In this series, 19 eyes of 11 patients had normal intraocular pressures and decreased facility of outflow. Three of these patients had unilateral decreased facility of outflow and normal tension and exhibited elevated intraocular pressure in the other eye. In six of the patients with bilateral decreased facility of outflow in spite of normal tensions, the diagnosis of glaucoma was confirmed by finding a glaucomatous field loss, by a positive result in the water-drinking test, or by subse-

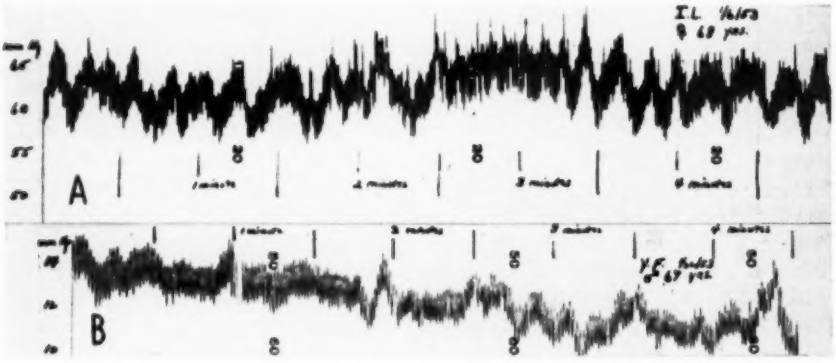

Fig. 3.—Tonographic tracings in eyes with untreated open-angle glaucoma. Scale at left represents intraocular pressure (P_o) in (*A*) an eye with elevated intraocular pressure and (*B*) an eye with "soft glaucoma."

quent elevations of tension. The two other patients with bilateral decreased outflow have shown no other evidence of glaucoma to date and must be classified as normal.

2. Narrow-Angle Glaucoma: Tonography in cases of this type revealed normal values between attacks unless there were extensive residual anterior synechiae. The tonographic evidence of synechiae in some such cases paralleled the gonioscopic findings, but often numerous synechiae produced no abnormality in the tracing. During acute attacks, the facility was greatly reduced, but outflow was normal or only slightly decreased. Goldmann has noted a striking reduction in facility of outflow during attacks, but his fluorescein method revealed an increased secretion and outflow. He reported this to be the case also in chronic congestive glaucoma. It must be recalled that the possibilities of increase in iris permeability would increase the turnover of fluorescein in just these cases. On the other hand, the underestimation of facility of outflow by tonography may result in false-low readings for flow.

3. Secondary Glaucoma: Tonography revealed decreased facility of outflow in proportion to the elevated tension. The total outflow was normal or somewhat

diminished. Here, again, Goldmann is in agreement that the facility is reduced but finds occasionally increased outflow. The question of permeability of the blood-aqueous barrier must also be raised in cases of this type, as must that of the errors of calculation in tonography.

4. "Glaucoma Due to Increased Secretion": Five female patients with constantly elevated tensions (30 to 40 mm. Hg), but with high normal values for facility of outflow, have been studied. In four of these the condition was bilateral, with no loss of vision or field. One patient had this condition in one eye, with normal facility of outflow, and open-angle glaucoma in the other eye, with similarly elevated pressure but decreased facility of outflow. It is of special interest to note that there was glaucomatous field loss only in the eye with decreased facility of outflow. The questions naturally arise as to whether these eyes represent early stages of the disease, variants of the normal, or errors in measurement. Corrections for blood pressure variations were not available when these women were studied. It is planned to reexamine them with continuous blood pressure tracings. There was no marked deviation from average values for corneal curvature or scleral rigidity in any of these eyes.

B. Effects of Provocative Tests for Glaucoma on Tonography.—1. Water-Drinking Test: The effect of water drinking has been studied in patients with an early or questionable diagnosis of open-angle glaucoma. In most instances (28 eyes of 16 patients) a positive reaction consisted of an elevation in pressure with an associated induced decrease in facility of outflow. In rare instances the facility remained normal and the tension rose significantly. This occurred in four eyes of two women which showed no other evidence of glaucomatous disease. These four eyes were, therefore, converted to the picture of "increased-secretion glaucoma." Further observations are needed to decide whether the results in these eyes represent true early glaucoma, merely a false-positive reaction to the provocative test, or a blood pressure effect.

Much more significant were those few eyes in which the tension remained normal but facility of outflow was diminished to levels below normal one hour after the ingestion of 1 liter of water. In a sense, the tonographic picture of "low-tension glaucoma" was induced in these eyes by the provocative test. This effect was noted in 10 eyes of 8 patients. Three of the patients with the unilateral effect in this group had open-angle glaucoma in their other eye. One patient with unilateral and two with bilateral effect had tensions in the 40-mm. range weeks to months afterward. Two patients with unilateral "low-tension glaucoma" had typical glaucoma field defects. It is such cases that can be picked up most readily by combining water drinking with tonography as a provocative test.

2. Dilatation of Pupil: In narrow-angle glaucoma, dilatation of the pupil frequently produced a rise in intraocular pressure with an associated decrease in facility of outflow. In two instances, however, no change in intraocular pressure was recorded, but a marked decrease in facility of outflow was induced. Here, again, the tonographic findings of "low-tension glaucoma" were induced. In one of these cases this occurred unilaterally; the other eye had had iridencleisis for acute congestive narrow-angle glaucoma. In the other the effect was bilateral and the angles were very narrow.

C. Evaluation of Therapy and Tonography.—1. Medical Therapy: Miotics usually improved facility of aqueous outflow in eyes with open-angle glaucoma, and

this was associated with a decreased intraocular pressure (74 eyes of 44 patients). There were a significant number (29 eyes of 19 patients), however, in which the pressure was normalized without improvement of facility of outflow. From the tonographic point of view, these eyes were changed to the findings in "soft glaucoma." This is a convenient mode of considering their status, for it raises the question of the adequacy of the therapy in such cases. It should be noted that in some instances (five eyes of four patients) increasing the frequency or concentration of the miotic therapy improved the facility of outflow to within normal limits. It would be premature to draw conclusions at this time as to the therapeutic implications of the finding of a controlled tension but an abnormally decreased facility of outflow. These 19 patients must be followed closely for long periods in order to determine whether field or vision will be lost under these circumstances. One would expect that such eyes would be much more susceptible to rises in pressure. In the brief follow-up period that has been possible to date, findings in three of these patients are of note. In one, with bilateral involvement, field has been lost in both eyes, although there was no recorded elevation of pressure. A second patient has lost field in the one eye with decreased facility of outflow, while the fellow eye, with facility increased to normal, did not lose field. Both eyes were receiving the same medication and running identical pressures. In the third patient the glaucoma was well controlled on miotics, with normal pressure and facility. On two consecutive occasions the facility was found to be decreased to abnormal values without any increase in intraocular pressure. Three weeks later, in spite of more intensive miotic therapy, the tension rose to the high 30's in both eyes. It would appear that the decreased facility represented a warning signal in this patient. At any rate, it may be concluded at present that those eyes in which facility remains decreased after miotic therapy should be followed more closely, and perhaps should receive more intensive therapy.

Phenylephrine (Neo-Synephrine) has been found to lower the tension slightly in normal eyes without change in facility of outflow. This may be merely the vascular effect of decreasing the total blood in the eye, or possibly of a change in outflow. Goldmann has noted decreased turnover of fluorescein after local administration of epinephrine. In some glaucomatous eyes phenylephrine has improved facility of outflow and decreased the intraocular pressure.

2. Surgical Therapy: Iridectomy in "normal" cataract patients has been reported by Grant to produce no change in facility or rate of outflow. In narrow-angle glaucoma, Grant's observations were readily confirmed, namely, that iridectomy produced an improvement in facility of outflow to normal levels. Goldmann has noted the same changes in facility, but, in addition, has noted a decreased outflow of aqueous for some months after surgery. Changes in permeability, again, may account for this discrepancy.

Successful iridencleisis and trephination have been found to improve facility of outflow as measured by tonography. From a few observations, it would appear that among the first signs of failure of a filtration bleb to function is a progressive decrease in facility of outflow.

Cyclodialysis improved facility of outflow as measured by tonography in most cases. Some patients, however, were noted to have a satisfactory reduction of intra-

ocular pressure but little, if any, improvement in facility of outflow. This may represent an abnormal facility state, or merely the tonographic representation of the marked persistent decrease of outflow following cyclodialysis reported by Goldmann. The filtering bleb or opening into the suprachoroidal space provides an enormous mode of outflow and prevents the assigning of a satisfactory value to the outflow pressure ($P_O - P_V$). This precludes the conversion of tonographic facility measurements to outflow values for these postoperative eyes. Values for outflow in these instances must, therefore, depend upon the determination of fluorescein turnover.

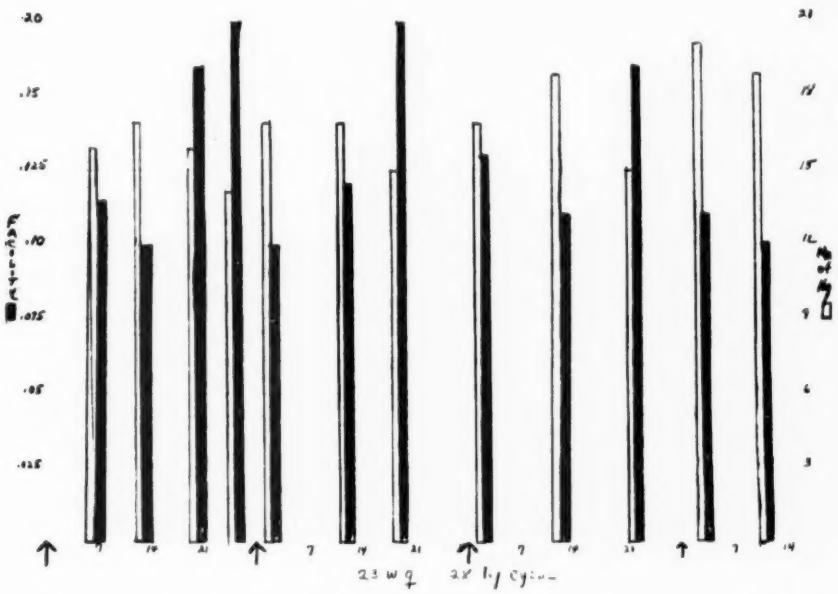

Fig. 4.—Variations in facility of outflow (solid bars) and intraocular pressure (open bars) in the left eye of a 23-year-old normal woman with a regular 28-day menstrual cycle. Arrows indicate onset of menses.

Retrociliary diathermy [16d, b] has been reported to produce a marked decrease in outflow with no change in facility of outflow. It would appear likely that this represents a decreased flow of aqueous or blood through the eye.

D. Physiological Variations with the Menstrual Cycle and Pregnancy.—Salvati [17] in 1923 noted an increase in intraocular pressure during menstruation. As reported by Shahan,[18] a small but definite cyclical variation in facility of outflow and in intraocular pressure with the menstrual cycle can be recorded tonographically with regularity in some normal women. In our experience, most women demonstrate a rela-

17. Salvati, M.: L'influence de la menstruation sur la tension oculaire, Ann. ocul. **160**:568, 1923.

18. Shahan, P. T., paper read before the Association for Research in Ophthalmology, Inc., Chicago, June, 1952.

tively increased facility of outflow during progestational phases of their menstrual cycle and a decreased facility during the estrogenic postmenstrual period. Small variations in pressure accompanied these changes (Fig. 4). Marx [19] first noted a fall in intraocular pressure early in pregnancy. With the cooperation of the Women's Clinic of The Johns Hopkins Hospital, tonographic tracings of normal pregnant women throughout their pregnancies have been obtained. These records usually reveal hypotony, and almost always presented a markedly increased coefficient of facility of outflow. Values for C of 0.35 to 0.55 were not unusual. This work is still in progress, and to date two women have delivered. It is in these patients that one can best appreciate the changes in ocular tension and facility of outflow that were associated with pregnancy. These two women had repeated recorded tensions of 10 to 13 mm. Hg during pregnancy and 16 to 18 mm. Hg after delivery. The facility of outflow in these subjects decreased from values of 0.33 to 0.42 during pregnancy to values of 0.23 to 0.28 in the nonpregnant states.

The association of the progestational phase of menstruation and of pregnancy with increased facility of outflow suggested a possible hormonal effect on intraocular pressure. From the nature of the changes noted above, progesterone appeared to be a likely choice. To date, 10 patients with glaucoma completely uncontrolled by miotics who had repeatedly refused surgical treatment have been treated with progesterone [20] at the Wilmer Ophthalmological Institute. During such therapy no change was made in the patients' miotic routine. Of the six men, two were entirely uninfluenced by therapy, and two experienced temporary lowering of intraocular tension for three and seven weeks, respectively, only to have it rise again. Increased dosage produced no benefit. Four women have been treated. One of these women, with aphakic glaucoma, has been followed for over fourteen months on oral therapy, with ocular tension and facility of outflow improved to within normal limits. Two women, who had each lost one eye from absolute glaucoma and had less than a 10-degree field in the remaining eye (not operated on), with tensions varying from 45 to 68 mm. Hg, have had the tensions kept down to levels of 28 to 34 mm. with oral use of progesterone for four months. The fourth woman, also one-eyed with advanced aphakic glaucoma, had had three operations for glaucoma, and for several months her tension could not be brought below 50 mm. by any miotic therapy, including use of diisopropyl fluorophosphate. She was admitted to the Wilmer Ophthalmologic Institute for cyclodiathermy, but the night before operation she was given an injection of 50 mg. of progesterone. The tension fell promptly from 50 to 14 mm. Hg. A cyclodialysis was performed, and her tension is well controlled at the moment. Similar single injections in two men before operation have been entirely without effect. The use of progesterone in the treatment of glaucoma is not new. It was first reported by Obal [21] in 1950, who noted some improvement in almost all of 37 patients, both male

19. Marx, E.: L'influence de la menstruation et de la grossesse sur la tension oculaire, Ann. ocul. **160**:873, 1923.

20. The progesterone used in these experiments was supplied by Organon, Inc. It was used in oral doses (Progestoral) of 25 to 200 mg. a day, or in intramuscular doses of 25 to 50 mg.

21. Obal, A.: Gelbkörperhormon-Anwendung zur Glaukomtherapie, Klin. Monatsbl. Augenh. **117**:201, 1950.

and female. Posthumus [22] reported successful lowering of intraocular pressure in all of 13 patients with glaucoma (6 males). Its use appears to be entirely without toxicity or side-effects. An extensive, carefully controlled clinical trial would, therefore, appear indicated.

SUMMARY AND CONCLUSIONS

The sources of error inherent in tonography are discussed and compared with those of other methods available.

The possibilities of correcting for the errors introduced by variations in corneal curvature, scleral rigidity, and, especially, blood pressure are described.

Tonography has proved itself of value clinically in the diagnosis of glaucoma; when combined with provocative tests, it offers unique opportunities for early diagnosis.

Evaluation of medical and surgical therapy may be greatly aided by repeated tonographic tracings.

The increased facility of outflow demonstrated by women in progestational phases of the menstrual cycle and pregnancy suggests the possible effect of some hormones on intraocular pressure.

22. Posthumus, R. G.: Use and Possibilities of Progesterone in the Treatment of Glaucoma, Ophthalmologica **124**:17, 1952.

MECHANISM OF THE MIOTIC-RESISTANT PUPIL WITH INCREASED INTRAOCULAR PRESSURE

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MYDRIASIS is one of the characteristic clinical signs of acute congestive (narrow-angle) glaucoma. It has long been known that in certain instances treatment with miotics of any type fails to bring about miosis or reduction in ocular tension. In such fulminating attacks, therefore, surgery must be performed under the adverse circumstances associated with high ocular tension, hyperemia, and congestion. This paper reports the results of investigations undertaken to determine the mechanism responsible for the miotic-resistant, dilated pupil of acute congestive (narrow-angle) glaucoma and to present certain possibilities regarding its origin.

The most likely explanations are (1) increased tone of the dilator muscle as a result of reflex stimulation of the sympathetic nerves; (2) pressure paresis of the parasympathetic motor nerves to the iris sphincter as they pass through the suprachoroidal space; (3) disturbance of the local neurohumoral mechanism, resulting in interruption of stimuli to the muscle cells of the iris sphincter, and (4) pressure upon the muscle cells of the iris sphincter, rendering them incapable of contraction.

The possible sites of these disturbances, in either the sympathetic or the parasympathetic pathways, can be visualized by studying Figure 1.[1] The upper left (unbroken) circle represents the site of the cell body of the sympathetic motor fibers in the cerebral cortex or the parasympathetic fibers in the Edinger-Westphal nucleus. The central (broken) circle represents the site of synapse in the two systems, the sympathetic superior cervical ganglion and the parasympathetic ciliary ganglion. A postganglionic fiber in either system supplies the muscle cells across a myoneural junction.

Human and animal studies were made to investigate each of the possible sites of disturbance and the explanations for the miotic-resistant pupil.

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Adapted from a thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania for the Degree of Master of Medical Science (M.Sc.[Med.]) for graduate work in ophthalmology (Dr. Tyner).

1. Scheie, H. G.: The Treatment of Primary Glaucoma by Medical Means, Tr. Am. Acad. Ophth. **53**:190 (Jan.-Feb.) 1949.

EXPERIMENTAL WORK

1. *Increased Tone of the Dilator Muscle as a Result of Reflex Stimulation of the Sympathetic Fibers.*—It is generally believed that pupillary dilatation following painful stimuli is due entirely to diminution of tone of the oculomotor nerve center, although some investigators (Gullberg, Olmsted, and Wagman) maintain that the

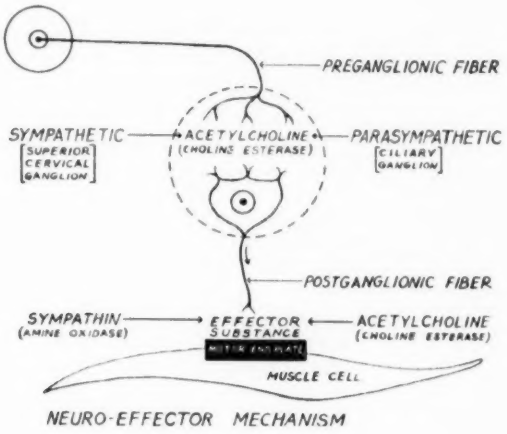

Figure 1.

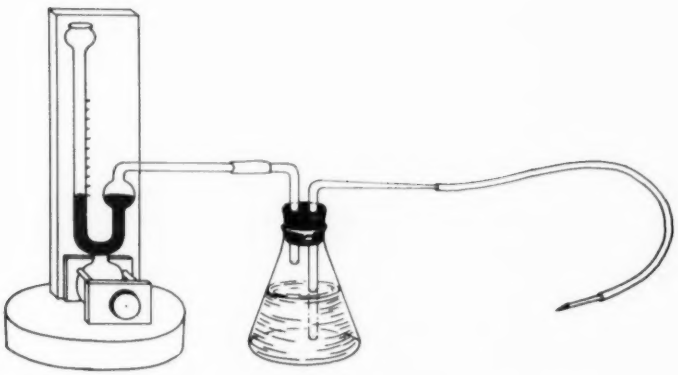

Fig. 2.—Apparatus devised to elevate the intraocular pressure.

sympathetic system participates in reflex dilatation of the pupil.[2] Fulton[3] cites evidence that reflex responses of the iris producing changes in pupillary diameter are mediated largely, if not solely, through the parasympathetic pathway.

2. Adler, F. H.: Physiology of the Eye: Clinical Application, St. Louis, C. V. Mosby Company, 1950, p. 145.

3. Howell, W. H.: Textbook of Physiology, edited by J. F. Fulton and others, Philadelphia, W. B. Saunders Company, 1949, p. 231.

The first explanation was ruled out on the basis of the opinions cited above and after one of us (H. G. S.) had failed to produce miosis in patients during attacks of acute narrow-angle glaucoma by injecting the cervical sympathetic chain with procaine. All the clinical signs of Horner's syndrome were produced except miosis. If the dilated pupil had been due to reflex stimulation via the sympathetic pathway, miosis should have been produced by the sympathetic block.

2. Pressure Paresis of the Parasympathetic Motor Nerves to the Iris Sphincter as They Pass Through the Suprachoroidal Space.—We believed this explanation could be ruled out by denervating pupils of dog eyes at various levels, constricting the pupils with miotics which acted directly upon the sphincter muscle, and then artificially raising the intraocular pressure. We found that the denervated pupils dilated after constriction with miotics when the tension was elevated above a critical

TABLE 1.—*Effect of Miotics on Pupillary Size in Eyes Subjected to Pressure of 60 to 80 Mm. Hg (Schiøtz) with Tension Elevated for One-Half Hour Prior to Instillation of Drug*

Time	Pupillary Size, Mm.	Tension, Mm. Hg	Drug	Comment
		Averages for Six Eyes		
1000	2	17	None	Initial tension
1005	..	..	.....	Tension elevated
1010	5-8	60	Physostigmine, 1%	One drop q. 5 min., 6 ×
1040	5-8	60	.....	Drug discontinued
1140	5-8	60	.....	One-hour observation
1145	0.5	10	.....	Tension lowered; immediate miosis, 1 sec.
		Average for Three Eyes		
1000	2	17	None	Initial tension
1005	..	..	.....	Tension elevated
1010	5-8	60	Pilocarpine, 1%	One drop q. 5 min., 6 ×
1040	5-8	60	.....	Drug discontinued
1140	5-8	60	.....	One-hour observation
1145	0.5	10	.....	Tension lowered, immediate miosis, 1 sec.

level. Thus, it was evident that pressure paresis of the motor nerves was not a factor in the pupillary dilatation with increased intraocular pressure.

A simple apparatus was devised to elevate artificially the intraocular pressure in dog eyes (Fig. 2). Saline or air was injected into the vitreous through a closed system connected to a mercury manometer. The intraocular pressure was raised to any desired level, and constant readings were obtained in millimeters of mercury.

Preliminary experiments were done to determine the level of intraocular pressure in dog eyes in which pupillary dilatation occurred. In the pentobarbital-anesthetized dog, with a pupil of 3 mm., the intraocular pressure was rapidly raised to 60 mm. Hg. The clinical picture of acute congestive glaucoma ensued. Clouding of the cornea and beginning pupillary dilatation occurred simultaneously with elevation of the pressure. At this pressure the pupillary diameter consistently reached 5 to 7 mm. within five minutes.

As long as the pressure was maintained at a constant level, the amount of pupillary dilatation remained constant. If the intraocular pressure was maintained in excess of 60 mm. Hg for 90 minutes, miosis could not be obtained with either pilocarpine or physostigmine, even though the drug was instilled at five-minute intervals over a period of 30 minutes (Table 1).

If miosis was produced by pilocarpine prior to elevating the pressure, mydriasis still occurred as the tension was raised (Table 2). Regardless of the drug used, miosis could be obtained only if the intraocular pressure was allowed to return to normal. The pupillary response to light was diminished or absent throughout the period of increased tension.

In order better to determine the relation of pupillary size to various levels of intraocular pressure, we carried out further experiments. When a moderately

TABLE 2.—*Effect of Miotics on Pupillary Size in Eyes Subjected to Pressures of 60 to 80 Mm. Hg (Schiøtz) with Miosis Obtained Prior to Elevation of Tension*

Time	Pupillary Size, Mm.	Tension, Mm. Hg	Drug	Comment
1000	3	17	Physostigmine, 1%	One drop q. 5 min., 6 ×
1030	1	17	.....	Drug discontinued
1100	1	17	.....	Pressure elevated
1103	5-8	60	.....	.....
1130	5-8	60	Physostigmine, 1%	One drop q. 5 min., 6 ×
1200	5-8	60	.....	Drug discontinued
1300	5-8	60	.....	One-hour observation
1305	0.5	10	.....	Pressure lowered
1000	3	17	Pilocarpine, 1%	One drop q. 5 min., 6 ×
1030	1	17	.....	Drug discontinued
1100	1	17	.....	Pressure elevated
1103	5-8	60	.....	.....
1130	5-8	60	Pilocarpine, 1%	One drop q. 5 min., 6 ×
1200	5-8	60	.....	Drug discontinued
1300	5-8	60	.....	One-hour observation
1305	0.5	10	.....	Pressure lowered

TABLE 3.—*Effect of Moderate Increase in Intraocular Tension* Over Four-Hour Period on Pupillary Size and Response to Light When Tension Was Raised by Injecting Saline into the Vitreous*

Time	Pupillary Size, Mm.	Tension, Mm. Hg	Drug	Comment
1030	2	15	None	Initial tension (Schiøtz)
1035	2	45	None	Mercury manometer reading
1100	2.5	45	None	Prompt light reaction
1130	2.5	45	None	Diminished light reflex
1200	3	45	None	Diminished light reflex
1230	2	45	None	Diminished light reflex
1300	2	45	None	Diminished light reflex
1330	2.5	45	None	Light reflex almost absent
1400	2.5	45	None	Light reflex almost absent
1430	2.5	45	None	Light reflex almost absent

* Constant readings in millimeters of mercury by manometer.

increased intraocular pressure of 45 mm. Hg was maintained over a period of four hours, no clouding of the cornea and no significant pupillary dilatation occurred (Table 3). An intraocular pressure of 60 mm. Hg was maintained for two hours. The pupillary diameter gradually increased from 2 to 5 mm. The pressure was then raised to 100 mm. Hg for a period of one hour. The pupil slowly increased in diameter to 6 mm. One per cent physostigmine salicylate was instilled every five minutes for six doses with the pressure at 100 mm. No change in pupillary size occurred. Pilocarpine was then instilled in similar manner, without effect. During the ensuing 90 minutes the pressure was gradually reduced to 80, 60, and 40 mm.

Hg. Definite decrease in pupillary size was first noted at 60 mm. Hg, with good miosis occurring as soon as the pressure was allowed to fall below the 60-mm. level (Table 4).

From these experiments it is evident that mydriasis occurs at a pressure of approximately 60 mm. Hg. This pressure level represents the critical point, in eyes

TABLE 4.—*Effect of High Pressure Gradients on Pupillary Size and Light Reflex*

Time	Pupillary Size, Mm.	Tension, Mm. Hg	Drug	Comment
1000	2	15	None	Initial tension (Schiøtz)
1015	3	60	None	Manometer reading
1045	4	60	None	.....
1130	5	60	None	.....
1200	5	60	None	.....
1201	5	100	None	.....
1230	5	100	None	Light reflex absent
1235	6	100	None	.....
1300	6	100	None	.....
1305	6	100	Physostigmine, 1%	One drop q. 5 min., 6 ×
1330	6	100	.....	Drug discontinued
1335	6	100	Pilocarpine, 1%	One drop q. 5 min., 6 ×
1405	6	100	.....	Drug discontinued
1410	5	80	.....	.....
1415	5	80	.....	.....
1440	5	80	.....	.....
1445	2	60	.....	.....
1515	2	60	.....	Pupillary size constant; pressure constant, 60 mm., 1 hr.
1516	0.5	40	.....	Immediate miosis
1520	0.5	40	.....	.....

TABLE 5.—*Effect of Increased Intraocular Pressure on Pupil Denervated by Retrobulbar Procaine* *

Time	Pupillary Size, Mm.	Tension, Mm. Hg	Drug	Comment
1030	2	15	None	Initial tension
1040	2	15	Procaine, 4%	2 cc. as retrobulbar block
1050	8	15	Pilocarpine, 10%	One drop q. 5 min., 6 ×
1115	1	15	.....	.....
1120	4	100	None	Immediate pupillary dilatation
1125	5	100	None	Pressure constant
1130	5	80	.....	.....
1200	5	80	.....	.....
1205	5	60	.....	.....
1210	2	60	.....	.....
1215	2	60	Procaine, 4%	Retrobulbar block repeated
1220	2	60	.....	.....
1230	1	60	.....	.....

* This table represents the averages for three eyes.

of the dog, at which the iris becomes refractory to the use of miotics and the miotic action of previously instilled drugs is ineffective.

The pupils of three dog eyes were denervated by a retrobulbar block of 4% procaine hydrochloride. This produced in effect a ciliary ganglionectomy. The pupils were constricted with 10% pilocarpine nitrate applied topically. The intraocular pressure was then elevated. Prompt pupillary dilatation occurred as long as the pressure was in excess of 60 mm. Hg (Table 5).

The pupil of one dog was denervated at the preganglionic level by cutting the oculomotor nerve within the skull. After a recovery period of two weeks, the pupil was constricted with pilocarpine and the tension elevated. The pupil promptly dilated when the intraocular pressure was raised (Table 6). These experiments indicate that the pupillary dilatation with high intraocular pressure is independent of the preganglionic and postganglionic nerve supply.

3. *Disturbance of the Local Neurohumoral Mechanism Resulting in Interruption of Stimuli to the Muscle Cells of the Iris Sphincter.*—We attempted to investigate the possibility of a disturbance at the myoneural junction. If the muscle cell could be stimulated directly by some method other than the usual neurohumoral transmission, it seemed logical that, in effect, the myoneural junction could be considered by-passed.

TABLE 6.—*Effect of Increased Intraocular Pressure on Pupil Denervated by Intracranial Section of Third Nerve*

Time	Pupillary Size, Mm.	Tension, Mm. Hg	Drug	Comment
1000	10	15	Pilocarpine, 10%	One drop q. 5 min., 6 ×
1030	2	15	.....	Drug discontinued
1035	6	100	None	.....
1045	6	80	None	.....
1100	6	80	None	.....
1115	4	60	None	.....
1130	4	60	None	.....
1145	1.5	40	None	.....

TABLE 7.—*Effect of Calcium Ion on Pupillary Size in Four Normal Dog Pupils Subjected to Intraocular Pressures of 70 Mm. Hg*

Time	Pupillary Size, Mm.	Tension, Mm. Hg	Drug
2000	8	15	0.3 cc. 10% calcium gluconate injected into anterior chamber
2010	2	15	.....
2020	8	70	.....

It is known that calcium ions stimulate the muscle cell itself.[4] Aqueous, 0.3 cc., was replaced by a solution of 10% calcium gluconate in four normal dog eyes. The pupils contracted to a diameter of 1 to 3 mm. When the intraocular pressure was raised to 70 mm. Hg, pupillary dilatation occurred rapidly in all eyes (Table 7).

COMMENT

It seems apparent by a process of elimination that none of the first three explanations can account for the dilated, miotic-resistant pupil in acute glaucoma. When the intraocular pressure is raised to a sufficiently high level, the iris sphincter is incapable of contraction when stimulated by acetylcholine-like drugs or cholinesterase-inhibiting drugs, or directly by calcium ions. The inability of the sphincter to respond to stimuli is not related to the effect of pressure on the motor nerve supply or, apparently, to any direct effect of sympathetic stimulation. We therefore believe that the site of disturbance is at the level of the muscle cell itself.

4. Sollmann, T. H.: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, Philadelphia, W. B. Saunders Company, 1948, p. 787.

We are unable to state with certainty whether the paresis of the sphincter muscle is due to interference with blood supply or to the direct effect of the increased intraocular pressure upon the muscle cell. We are also unable to say whether the pupillary dilatation is active or passive. We have found by experiment that both the iris sphincter and the dilator muscles are capable of response to autonomic drugs after death and in enucleated eyes. Two per cent pilocarpine nitrate was instilled into the conjunctival sacs of 10 dog eyes after death. The pupillary diameter was reduced by 4 to 6 mm. over a period of two hours. Two normal human eyes were enucleated post mortem for corneal transplantation. Fifteen hours after death the pupils were 5 mm. in diameter. Pupillary constriction to 2 mm. was obtained by dropping a solution of pilocarpine on the enucleated eyes.

The intraocular pressure was raised in the 10 dog eyes and the two human eyes after the pupils were constricted. The pupils did not dilate. The pupils of six additional dog eyes were constricted ante mortem. The intraocular pressure was raised post mortem, but the pupils did not dilate. Failure to dilate rules out another possible explanation, mechanical stretching of the pupil due to forward movement of the vitreous and lens.

Ten per cent phenylephrine (Neo-Synephrine) hydrochloride was applied topically to one eye of four fresh human cadavers. The contralateral eye was used as a control. Moderate dilatation of the pupil occurred in 30 minutes after repeated instillations. In two cadavers the opposite pupil was miotic, as a result of the antemortem use of morphine. In one enucleated human eye the pupil dilated widely after copious application of the drug.

The ability of the pupils of enucleated eyes and of fresh cadaver eyes to respond to autonomic drugs is presumptive evidence against interruption of blood supply as a cause of the paretic pupil when the intraocular pressure is elevated. We are quite certain, however, that high pressure does damage the sphincter, perhaps by repeated or prolonged ischemia. We have examined the eyes of patients who have had acute glaucoma and have found that a fairly significant percentage have rather severe marginal atrophy of the iris near the pupillary border, which might well result from ischemia or poor nutrition.

SUMMARY

A report is made of studies undertaken to determine the mechanism responsible for the miotic-resistant, dilated pupil seen in some cases of acute narrow-angle glaucoma. Five possible explanations for the phenomenon are considered: (1) increased tone of the dilator muscle as a result of reflex stimulation of the sympathetic fibers; (2) pressure paresis of the parasympathetic motor nerves to the iris sphincter as they pass through the suprachoroidal space; (3) a disturbance of the local neurohumoral mechanism, resulting in interruption of stimuli to the muscle cells of the iris sphincter; (4) the effect of pressure upon the muscle cells of the iris sphincter, rendering them incapable of contraction, and (5), as suggested in Comment, mechanical stretching of the pupil by forward movement of the vitreous and lens.

By a process of elimination based on clinical and experimental observations, all but the fourth explanation are ruled out. As a result of these studies, we believe that mydriasis due to increased intraocular pressure occurs as a result of depression of the function of the muscle cell itself. We have, so far, been unable to demon-

strate the mechanism whereby the mechanical effect of pressure renders the iris sphincter incapable of contraction. It seems apparent that a critical level of increased intraocular pressure exists at which the pupil no longer will respond to miotics. In dogs this level is in the neighborhood of 60 mm. Hg.

Human and dog pupils will respond to autonomic drugs after death. Pupils which are constricted by pilocarpine after death will not dilate when the pressure is elevated, as will pupils in living eyes.

CONCLUSIONS

The site of disturbance responsible for the dilated, fixed, miotic-resistant pupil seen in attacks of acute narrow-angle glaucoma is at the level of the muscle cell itself. The mydriasis seen with increased intraocular pressure is independent of the preganglionic and postganglionic motor nerve supply to the iris sphincter, the local neurohumoral mechanism, and, probably, the sympathetic stimulation of the dilator muscle. A critical level of increased intraocular pressure exists at which the pupil will no longer respond to miotics and will not constrict unless the pressure is lowered by other means. The pupils of fresh human cadavers will respond to pilocarpine and phenylephrine (Neo-Synephrine) but will not dilate with increased intraocular pressure.

AQUEOUS OUTFLOW MEASUREMENTS BY CONTINUOUS TONOMETRY IN SOME UNUSUAL FORMS OF GLAUCOMA

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IOWA CITY

IT HAS been known for a long time that the continuous application of external pressure to the eye produces a decrease in the intraocular tension. The response of healthy eyes to this so-called massage effect was thought to differ characteristically from the response of eyes with glaucoma. In the past, numerous investigators have attempted to utilize this difference as a clinically useful tool in the diagnosis of glaucoma. At first, the dynamometer of Bailliart was used to apply pressure to the eye, and the tension was taken with an ordinary tonometer. Interpretation of the data obtained in such a manner was hindered by a lack of understanding of the relation between intraocular pressure and volume of ocular contents. It was not until the work of Friedenwald [1] in 1937 and 1939 that these relationships were clarified. He devised a table giving the volume of the corneal indentation and the intraocular pressure corresponding to different scale readings and plunger loads of the Schiøtz tonometer. Another technical advance was the development of an electronic tonometer, permitting the accurate application of a corneal indenting force and simultaneous readings of the intraocular tension.

When a tonometer of the Schiøtz type is applied to the eye, the impingement of the plunger produces a localized indentation of the cornea and the displacement of a small amount of intraocular fluid. The resistance of the wall of the eyeball to this distending force causes an initial rise in intraocular pressure. This rise in pressure produced by the application of the tonometer is expressed by the symbols P_o and P_t, the former signifying the pressure before, and the latter signifying the pressure during, the application of the tonometer. Conversion tables supplied by the manufacturers of tonometers read in P_o values only. P_t values for each tonometer reading can be obtained from a table devised by Friedenwald,[2] who made systematic P_t measurements over the ordinary range of P_o values.

Almost as soon as the tonometer is applied to the cornea, the scale reading begins to rise, indicating an increase in the depth of indentation and a loss of ocular fluid from the eye. Prior to examination, the eye is assumed to exist in a steady state, with the intraocular pressure determined by the net rate of aqueous formation and the amount of resistance to its escape from the eye. This steady state is

Dr. Hermann M. Burian gave aid in the preparation of the manuscript.

From the Department of Ophthalmology, State University of Iowa College of Medicine.

1. Friedenwald, J. S.: Contribution to the Theory and Practice of Tonometry: Analysis of Work of Professor S. Kalfa with Applanation Tonometer: I, Am. J. Ophth. **20**:985, 1937; II, ibid. **22**:375, 1939.

2. Moses, R. A., and Bruno, M.: Rate of Outflow of Fluid from the Eye Under Increased Pressure, Am. J. Ophth. **33**:389, 1950.

disturbed by the increase in intraocular pressure caused by the application of the tonometer. The difference between the original pressure, P_o, and the artificially elevated pressure, P_t, represents the pressure increment disturbing the equilibrium which had existed prior to the test. The elevation of pressure forces fluid, presumably aqueous, out of the eye. The possibility that the total blood content of the eye is diminished during tonography must also be considered. Experimental evidence showing that this factor has only a minimal influence on the results of tonographic measurements was brought forth by Morton Grant.[3] His finding that the coefficient of facility of outflow was of the same magnitude for normal eyes as for eyes which were enucleated is especially significant in this regard.

When fluid is forced out of the eye, the total ocular volume decreases at a rate corresponding to the difference between the rate of loss and the rate of formation of aqueous. Assuming that the rate of aqueous formation does not significantly change during the examination, one can take the rate of decrease of ocular volume as an approximation of the rate of loss of aqueous. Friedenwald [4] has determined experimentally the volume change of the eye with various tonometer loads at all the ordinary scale readings, and the accuracy of all published data on aqueous outflow determined tonometerically depends on his work.

Most of the recent data on tonography have been calculated on the formulas used by Grant,[3] namely:

$$C = \frac{\Delta\ V}{(Avg\ P_t - P_o)\ time}$$

$$K = C\ (P_o - 4)$$

and Δ V is an expression obtained from Friedenwald's table, giving the volume displaced for the initial and final tonometer readings, by deducting the former from the latter. The average $P_t - P_o$ is obtained by determining the arithmetical mean of the initial and the final P_t and deducting from it the original P_o. The final result (C) is a volume-pressure ratio, called by Grant the "coefficient of facility of outflow." This coefficient represents the rate at which fluid can be expressed from the eye by pressure, in terms of cubic millimeters per minute per millimeter of pressure. The net rate of flow of aqueous in cubic millimeters per minute (K) can be obtained by multiplying the coefficient of outflow by $P_o - 4$. If steady-state conditions can be assumed to prevail, this rate is equal to the net rate of aqueous humor formation.

Grant [5] has simplified these calculations by devising a chart based on a tonographic measurement taken for four minutes with a 5.5-gm. tonometer weight. By plotting the initial and the final scale readings on this chart, one can read off directly the coefficient of outflow. This simplified technique is especially adaptable as a clinical tool in evaluating suspected cases of glaucoma.

The actual tonographic measurements are easily carried out. One or two drops of 0.5% tetracaine hydrochloride provides adequate anesthesia in older children and adults. I have the patient lie down, with the head comfortably supported, and take several pretest readings. When the prevailing P_o is determined, whether steady, rising, or falling, the electronic tonometer

3. Grant, W. M.: Tonographic Method for Measuring the Facility and Rate of Aqueous Flow in Human Eyes, Arch. Ophth. **44**:204, 1950.

4. Friedenwald, J. S.: Problems in the Calibration of Tonometers, Am. J. Ophth. **31**:935, 1948.

5. Grant, W. M.: Clinical Tonography, Tr. Am. Acad. Ophth. **56**:774, 1951.

is applied continuously to the patient's cornea for 5 minutes, and an assistant records the scale reading every 30 seconds. Infants and small children require a general anesthetic, and in these cases pretest readings are not taken.

Up to the present time I have made tonographic measurements on about 100 eyes. When practicable, the procedure was repeated two or three times on successive days. About 40 normal eyes were examined, the rest being glaucomatous eyes, treated and untreated, or eyes suspected of being glaucomatous. All the patients had a complete clinical examination, which included gonioscopy in the majority.

Figure 1 is a graphic representation of the range of the normal tonogram, with my average figures for *C* and *K*. Average figures reported by Grant [6] and by Kronfeld [7] are shown for comparison.

The scattergram in Figure 2 is a composite of all eyes I have examined which have not had operation or treatment of any kind.

For all patients with untreated glaucoma the outflow coefficient was under 0.20, being under 0.15 for the majority. A number of patients without clinical evidence

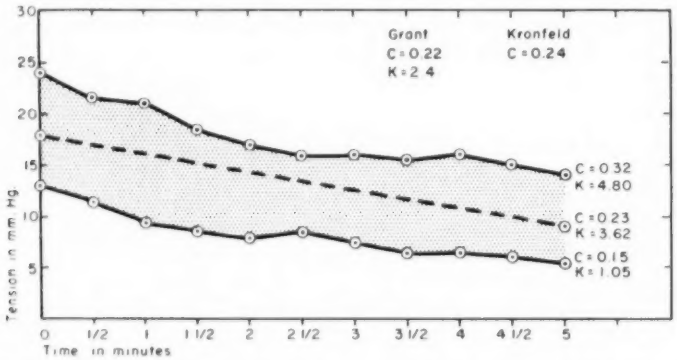

Fig. 1.—Normal tonographic range. The upper and lower lines represent the highest and lowest tonograms of the 40 normal eyes examined. The broken line represents the normal mean used in this study. The average figures of Grant [6] and Kronfeld [7] are listed for comparison.

of glaucoma and with tensions between 25 and 30 mm. (Schiøtz) revealed outflow coefficients under 0.18. These were classified as glaucoma suspects and will be reexamined at frequent intervals. A few of the normal patients showed outflow coefficients as low as 0.15, but the majority had coefficients above 0.20. These findings parallel the experience of Grant and Kronfeld.

Figure 3 is the tonogram in a typical case of wide-angle glaucoma. The coefficient of outflow is rather low before treatment and is still far below the normal even after the tension has been controlled on miotic therapy. The net rate of flow or production of aqueous is also abnormally low before and after treatment.

Figure 4 presents the tonogram of a unilateral glaucomatocyclitic crisis. Before treatment the outflow coefficient is low, and the net rate of aqueous production is also in the low-normal range. After remission of the episode the tonogram is essentially normalized. Grant has reported similar findings in these two types.

6. Grant, W. M.: Clinical Measurements of Aqueous Outflow, A. M. A. Arch. Ophth. **46**:113, 1951.

7. Kronfeld, P. C.: Tonography, A. M. A. Arch. Ophth. **48**:393, 1952.

The tonogram shown in Figure 5 is that of a patient with glaucoma secondary to uveitis. While the outflow coefficient is below normal, the rate of production of aqueous appears to be high. After cyclodiathermy, the tension has become normal-

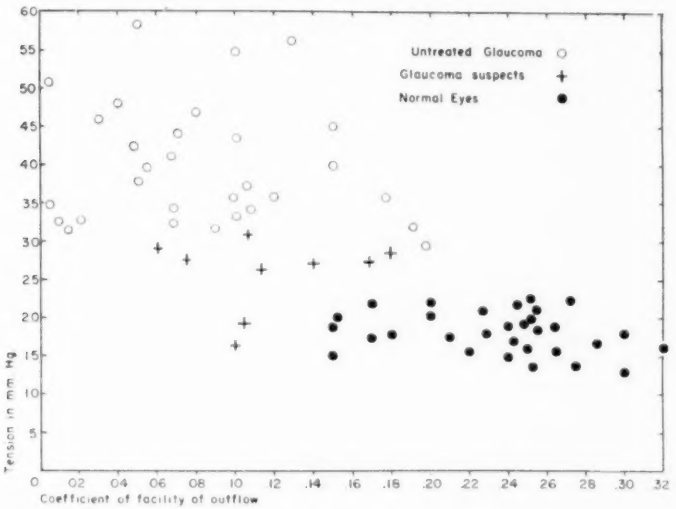

Fig. 2.—Scattergram of coefficient of facility of outflow in normal eyes, eyes suspected of being glaucomatous, and eyes with untreated glaucoma.

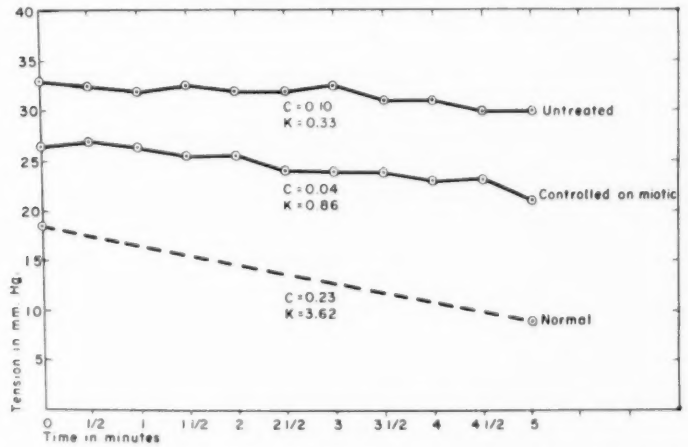

Fig. 3.—Tonogram in typical case of wide-angle glaucoma before and after treatment.

ized; the outflow coefficient is still abnormally low, and the production of aqueous is reduced. Friedenwald [8] has made the point that the error in calculation of K may be as much as ± 20 to 30%. Even assuming the maximum error, the initial hyper-

8. Friedenwald, J. S., in discussion on Grant,[6] p. 124.

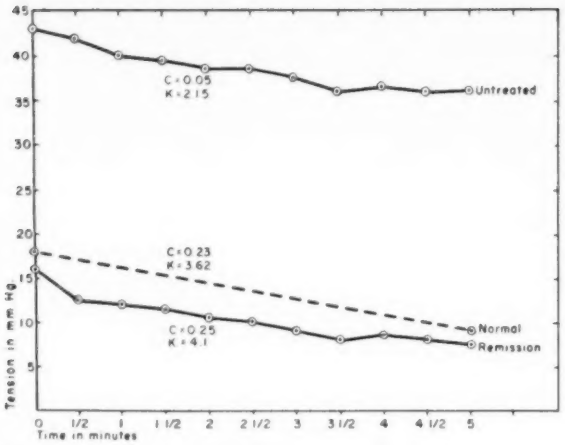

Fig. 4.—Tonogram of eye with glaucomatocyclitic crisis during attack and during remission.

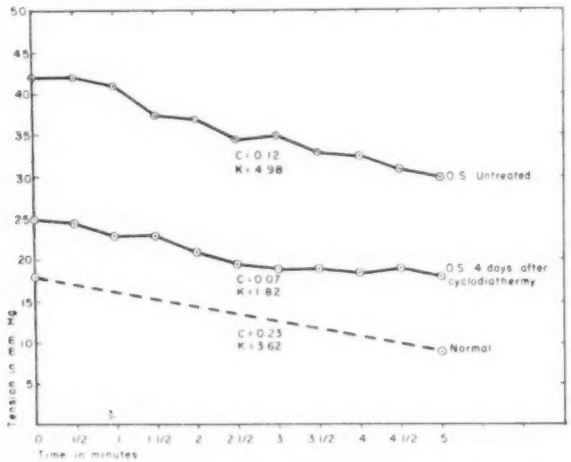

Fig. 5.—Effect of cyclodiathermy on tonogram of left eye of patient with glaucoma secondary to uveitis.

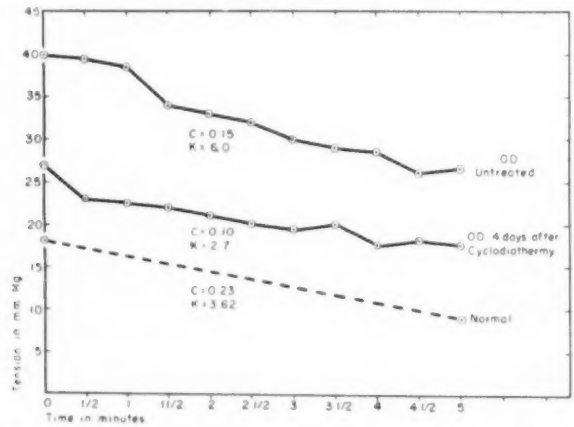

Fig. 6.—Effect of cyclodiathermy on tonogram of right eye of patient with glaucoma secondary to uveitis. (See Figure 5 for effect on left eye of the same patient.)

formation of aqueous and its reduction following the operation appear to be real. This patient's other eye also exhibited an elevation of tension and uveitis (Fig. 6). Here, again, the outflow coefficient is abnormally low, while the production of aqueous appears to be high before cyclodiathermy and definitely reduced afterward.

We were able to examine two children with the Sturge-Weber syndrome exhibiting unilateral glaucoma. Their tonograms are shown in Figure 7. Both patients

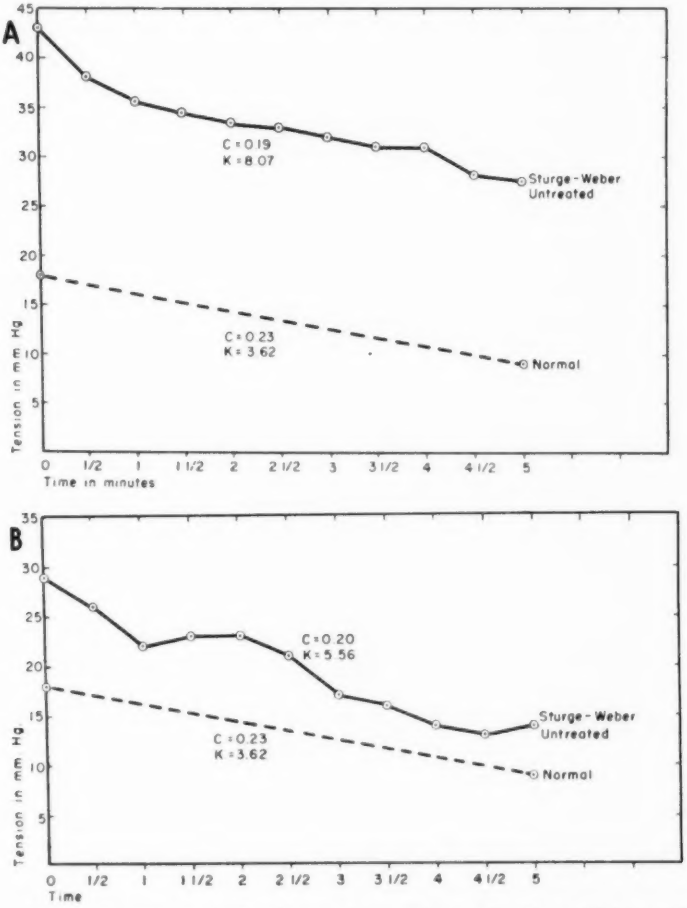

Fig. 7.—Tonograms of affected eye of two patients with Sturge-Weber syndrome.

exhibited an outflow coefficient in the normal range, with a relatively high production of aqueous. Figure 8 contrasts the findings in one of the cases of the Sturge-Weber syndrome with those in a typical case of buphthalmos. One notes in the latter the marked reduction in facility of outflow and the very low net rate of production of aqueous. These children were all of about the same age and had the same type of anesthetic when the measurements were made.

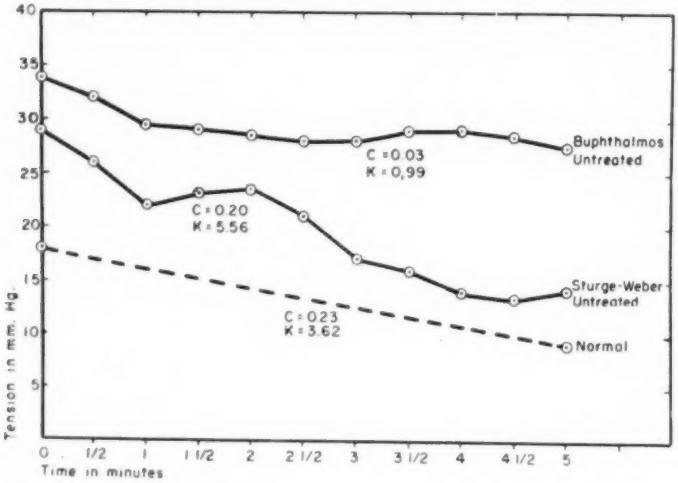

Fig. 8.—Comparison of tonogram of an eye with untreated buphthalmos, with tonogram of eye of patient with Sturge-Weber syndrome.

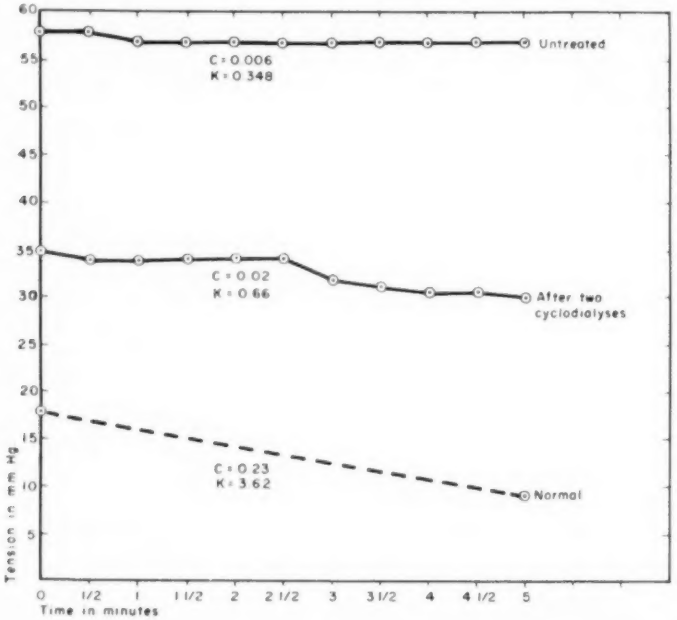

Fig. 9.—Tonogram of eye of adult patient with congenital abnormality of chamber angle, before treatment and after two cyclodialyses.

Figure 9 is the tonogram of a young man with a congenitally anomalous chamber angle. The outflow coefficient was extremely low before treatment and was still definitely in the abnormally low range even after two cyclodialyses. At the time of this examination one of the cyclodialysis clefts appeared to be open on gonioscopic examination.

CONCLUSIONS

The tonographic study of normal eyes and of glaucomatous eyes yielded average figures for the coefficient of aqueous outflow and the net rate of aqueous formation which were in close agreement with those of Grant and Kronfeld. This would point not only to a confirmation of the findings of these authors, but also to the fact that on the whole their technique was closely duplicated.

The results of tonography thus far reported in the literature would appear to substantiate the conclusion that the increased intraocular pressure in chronic simple glaucoma and in some forms of secondary glaucoma is the result of an obstacle to the outflow of aqueous. This was also evident in my studies, as may be seen from the cases illustrated in Figures 3, 4, 5, and 9. However, to date there has been no report citing tonographic evidence for excessive formation of aqueous in any type of glaucoma. Such evidence is now given for two eyes affected with glaucoma and naevus flammeus. This evidence is particularly impressive when the rate of aqueous formation in these eyes is compared with the rate of aqueous formation in a case of ordinary buphthalmos, a condition which has long been known to be due to obstruction or congenital abnormalities in the chamber angle.

Furthermore, in two eyes with secondary glaucoma associated with uveitis there also appeared to exist an excessive net rate of aqueous formation. After the tension was normalized by cyclodiathermy in these two eyes, the coefficient of facility of aqueous outflow was not improved, but there was a substantial drop in the rate of aqueous formation. The effect of cyclodiathermy on the net rate of formation of aqueous and the mechanism of this operation are at present under investigation.

SUMMARY

The principle and technique of tonography are described, and the average figures for the coefficient of facility of aqueous outflow and for the net rate of aqueous formation are given for normal eyes and for eyes with glaucoma.

Evidence is given that in some forms of secondary glaucoma (glaucoma in the Sturge-Weber syndrome; glaucoma secondary to uveitis) in which the coefficient of outflow was in normal range the elevated intraocular pressure was due to increased aqueous formation.

In the two eyes in which the intraocular pressure was normalized by cyclodiathermy, there was no tonographic evidence of improved aqueous outflow, but a substantial drop in the net rate of aqueous formation was observed.

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SIMPLIFIED PTOSIS SURGERY

Resection of the Levator Palpebrae by the External Route

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THE MANY operations published for correction of ptosis fall under three heads, involving utilization of (1) the frontalis muscle, (2) the superior rectus muscle, or (3) the levator palpebrae.

When there is complete paralysis of the levator muscle, a resection of this muscle will nearly always give an inadequate result. If the paralysis is bilateral, an operation of the Dickey [1] type may be done, attaching the lid to the superior rectus by means of a fascia lata sling.[2] This may often give a brilliant result, but a serious disadvantage is the consequent very defective lid closure during sleep and the impaired ability to wink. In addition, in some cases at the Massachusetts Eye and Ear Infirmary, troublesome hyperphoria has resulted. Since the superior rectus is attached to the lid in front of the axis of rotation, some reduction in lateral motion may also occur.

In cases of complete levator paralysis, my own preference for many years has been a modified Derby fascia lata sling operation, using a strip of fascia 4 mm. wide taken from the thigh. Preserved ox fascia was also tried in five cases. Elimination of the thigh incision simplified the procedure greatly, and the animal fascia ultimately gave satisfactory results; but reaction was pronounced, and in one case inflammation was so extreme that for several days there was danger of an extensive slough developing. Because of this, the use of ox fascia was discontinued.

SUTURE OPERATION

Since Friedenwald and Guyton [3] announced their first cases of simple suspension of the lid to the frontalis by purse-string sling sutures, I have relied entirely on some variation of this procedure in cases of complete paralytic ptosis and have abandoned all fascia lata surgery.

My very early suture operations, done with braided tantalum wire, were unsatisfactory, as the final amount of the correction was always considerably less than that obtained shortly after operation. In an attempt to have the final effect essentially the same as the immediate postoperative effect, the following operation was devised and reported in 1948.[4]

1. Dickey, C. A.: Superior Rectus Fascia Lata Sling in the Correction of Ptosis, Am. J. Ophth. **19**:660-664 (Aug.) 1936.

2. Cordes, F. C., and Fritschi, U.: Dickey Operation for Ptosis: Results in 21 Patients and 30 Lids, Arch. Ophth. **31**:461-468 (June) 1944.

3. Friedenwald, J. S., and Guyton, J. S.: Simple Ptosis Operation: Utilization of the Frontalis by Means of a Single Rhomboid-Shaped Suture, Am. J. Ophth. **31**:411-414 (April) 1948.

4. Leahey, B. D.: Simplified Ptosis Surgery, presented at joint meeting of the New England Ophthalmological Society and the Massachusetts Eye and Ear Infirmary Alumni, November, 1948.

A 1-cm. horizontal incision was made in the upper lid 2 mm. above the lashes. After the tissue was undermined upward, a piece of tantalum gauze mesh, 9 by 3 mm., was implanted. Two ¼-in. (6.4 mm.) horizontal incisions were made just above the eyebrow about ½ in. (1.27 cm.) apart, and tantalum gauze was also implanted in these locations. Two braided tantalum sutures were threaded through the lower piece of gauze and carried up under the skin and out through the tantalum gauze in the upper incisions. The skin incisions were closed and the

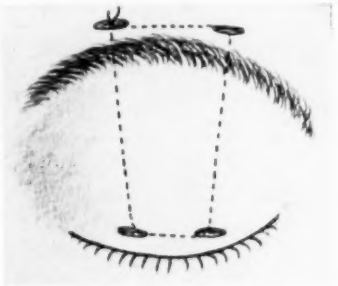

Fig. 1.—Diagram of Friedenwald-Guyton ptosis suture. This suture should be tightened before tying to give a temporary 2-mm. overcorrection.

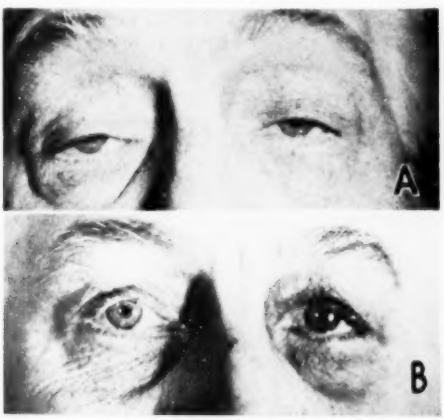

Fig. 2.—*A*, a 77-year-old woman with bilateral almost complete paralytic ptosis. She had worn crutch glasses for many years; *B*, appearance after placement of Friedenwald-Guyton sutures.

untied ends of the sutures left protruding upward, covered by a sterile dressing on the forehead (Fig. 3).

Ten days later, after the implanted gauze was firmly healed in place, the brow incisions were reopened down to the tantalum gauze, and the tantalum wires were pulled tight enough to raise the lids and tied. The ends were cut and carefully tucked in under the skin, and the tiny skin incisions were resutured. The patient was kept in the hospital only one day after each procedure. The object of the tantalum mesh, of course, was to anchor the tantalum wire and keep it from gradually cutting through the tissue later.

At the time of the original preliminary report, four of these operations had been done, with apparently excellent results. Six months later, however, mild low-grade inflammation began to show around the tantalum sutures in two of these cases, requiring removal of part of the sutures, but not the tantalum gauze. This procedure also was abandoned.

During the last five years, 24 suture suspension operations were done, using 2-0 white silk (nonabsorbable surgical) sutures. The results with this simple method have been extremely satisfactory; and, in my opinion, it is now the operation of

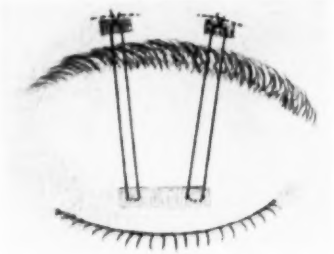

Fig. 3.—Correction of paralytic ptosis by use of braided tantalum sutures passed through tantalum mesh.

Fig. 4.—*A*, complete paralytic ptosis; *B*, one week after implantation of tantalum gauze and untied tantalum sutures; *C*, five days after tying tantalum sutures; *D*, two months later.

choice in all cases of pronounced ptosis without any levator action. White nylon should also be satisfactory. General anesthesia is used in these cases, as procaine infiltration interferes with the estimation of proper suture tightness and lid elevation.

The procedure is easy to perform; there is almost no postoperative reaction, and the patient may safely go home a few hours or one day after operation. If the procedure is not effective or the appearance is not completely satisfactory, it is a simple matter to take the suture out later and put in another; or one of the more standard ptosis operations may be done. In 5 of the 24 cases the operation was done a second time because of inadequate lid opening. In a sixth, the suture was

removed several months later because of chronic inflammation. In this case, however, connective tissue bands had formed along the track of the suture and the lid stayed open satisfactorily.

When ptosis is adequately corrected by this suture method, the frontalis muscle becomes more important in controlling the lid. Voluntary closure is good, and winking is satisfactory. The eyes remain open 2 or 3 mm. during sleep; but since the eye is not held to the lid, as in operations for ptosis using the superior rectus, and hence rotates upward freely, there are no complications from corneal exposure.

RESECTION OF THE LEVATOR

In my experience, in 70% of the cases of ptosis there is slight levator action, even though drooping may be pronounced. In these cases the operation of choice is a procedure which will increase the effectivity of the levator. Exposure of the levator may be either through the skin externally or through the conjunctiva by inversion of the lid. Since Blaskovics [5] brought out his excellent procedure, the conjunctival route has been the one most widely used by American surgeons. More recently, Berke [6] has published his modification of this technique. This procedure is very effective and is somewhat simpler than the original Blaskovics operation.

Iliff has a new, and even simpler, version than Berke's. Iliff [7] grasps the conjunctiva along with the muscle in his clamp and advances and resects the conjunctiva and the muscle simultaneously. Since his advancement sutures are inserted through the conjunctiva, they can be placed no higher than the upper fornix. It is probable that this procedure would give relatively better results in cases of slight or moderate ptosis than in cases of pronounced ptosis.

During my residency at the Massachusetts Eye and Ear Infirmary, 20 years ago, levator resections were done routinely via this conjunctival route. Surgeons considered the procedure more troublesome than the more routine cataract and strabismus operations and the results less satisfactory. Because of this, many excellent surgeons preferred not to do ptosis operations. It seemed that direct exposure of the levator through the lid would be the simplest approach for men doing only occasional ptosis operations; and from the early ophthalmic literature, it was obvious that many other surgeons had the same idea.

Shortening of the levator through a skin incision has been described by many authors over the past 70 years. In 1883 Everbusch [8] first described his tucking operation.[9] Two sutures were placed in the levator muscle. When these were carried out through the lid margin and tightened, a tuck in the muscle was carried down to the anterior surface of the tarsal plate. In 1903 de Lapersonne [10] brought

5. de Blaskovics, L.: Treatment of Ptosis: Formation of a Fold in the Eyelid and Resection of the Levator and Tarsus, Arch. Ophth. **1**:672-680 (June) 1929.

6. Berke, R. N.: A Simplified Blaskovics Operation for Blepharoptosis, A. M. A. Arch. Ophth. **48**:460-495 (Oct.) 1952.

7. Iliff, C.: Simplified Ptosis Surgery, presented at Residents Meeting, Wilmer Ophthalmological Institute, March, 1953.

8. Everbusch: Lid Shortening by Suture from Levator to Lid Margin, Monatsbl. Augenh. **13**:100, 1883.

9. Grimsdale, H. B., and Brewerton, E. W.: Textbook of Ophthalmic Operations, London, K. Paul, French, Trübner & Co., 1907, p. 58.

10. de Lapersonne, F.: Sur quelques modifications dans les operations du ptosis, Bull. et mém. Soc. franç. opht. **20**:383-389, 1903.

out his resection and advancement technique. This appears to be the first levator resection ever done. It has since become widely used throughout the world, although the technique is usually described in the literature as the "Everbusch operation." Since 1934 I have been using a modification of this procedure of de Lapersonne and consider it both technically easy and extremely effective.

Method.—A horizontal incision is made in the skin of the upper lid about 9 mm. above the lid margin, or four-tenths of the distance from lid margin to eyebrow. By means of blunt dissection with scissors, the gleaming white tarsal plate is exposed, and from then on the upper tarsal border is used as the main "landmark" (Fig. 6*A*). A horn lid spatula is inserted under the lid. The lid is pulled down, stretching the levator muscle, and the dissection is carried upward, exposing the levator for approximately 15 mm. above the upper border of the tarsus. On either side of the levator muscle just above the upper tarsal margin, a small opening is made with scissors tips completely through the lid and conjunctiva (Fig. 6*B*). A strabismus hook is introduced under the levator muscle and conjunctiva and brought out on the other side of the muscle, as in an ordinary strabismus operation (Fig. 6*C*). The levator is freed as far back as possible (usually about 1.5 cm.). In order to facilitate manipulation of the muscle, a Prince forceps is applied about 6 mm. above the upper tarsal border.

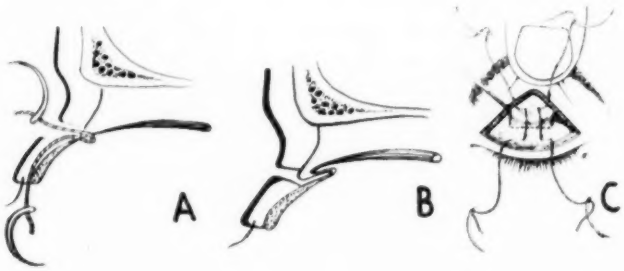

Fig. 5.—*A*, Everbusch's operation: suture looped through levator and brought down through lid margin. *B*, Everbusch's operation: folding of tendon produced by tying lid sutures. According to de Lapersonne and Fuchs, this procedure was suitable for slight ptosis but was inadequate in cases of pronounced ptosis. *C*, advancement of levator as done by de Lapersonne (1903). He did not cut through the conjunctiva and usually excised a small strip of skin from the lower lip of the wound.

Three lock 4-0 mild chromic catgut (absorbable surgical) sutures are inserted in the levator muscle above the Prince forceps (Fig. 6*D*). These should be put from 7 to 10 mm. above the upper tarsal border. Some authors, including Blaskovics, Berke, and Iliff, also resect a portion of the tarsus. This is quite unnecessary in the external-route operations. Since the levator is to be advanced down the tarsus, excision of tarsus above the new levator attachent can be of no avail. Furthermore, the intact tarsus provides stability of contour to the lid margin. When much tarsus has been resected, it is possible for the lid to show flexible "Gothic" arching, due to strong levator action, as well as an increasing tendency toward entropion or ectropion.

Each arm of the three double-armed catgut sutures is inserted in the upper portion of the tarsal plate, as in Figure 7*A* and tied.

Despite considerable shortening and advancement of the levator, the result will frequently be inadequate unless supporting stay sutures are inserted in the lid for at least six days after operation. Lack of suitable stay sutures has probably been the sole reason for the unsatisfactory results obtained by many surgeons in their ptosis cases. Incidentally, in their conjunctival-route techniques, both Blaskovics [5] and Berke [6] considered a 20-mm. resection necessary in the average case of pronounced ptosis. With the procedure being outlined here, 10 mm. is usually ample in a case of even a very extreme ptosis.

Before the skin is sutured, 5-0 black stay sutures are inserted through rubber buttons from 3 mm. above the line of eyelashes to 3 mm. above the eyebrow, as in Figure 7*B*, but these sutures are not tied until later.

The skin incision is then closed with approximately eight interrupted silk sutures of 5-0 and 6-0 black silk, spaced very close together so as to leave no visible scar. Two of these sutures are deeply placed to include some fibers of the advanced levator muscle (Fig. 7*C*).

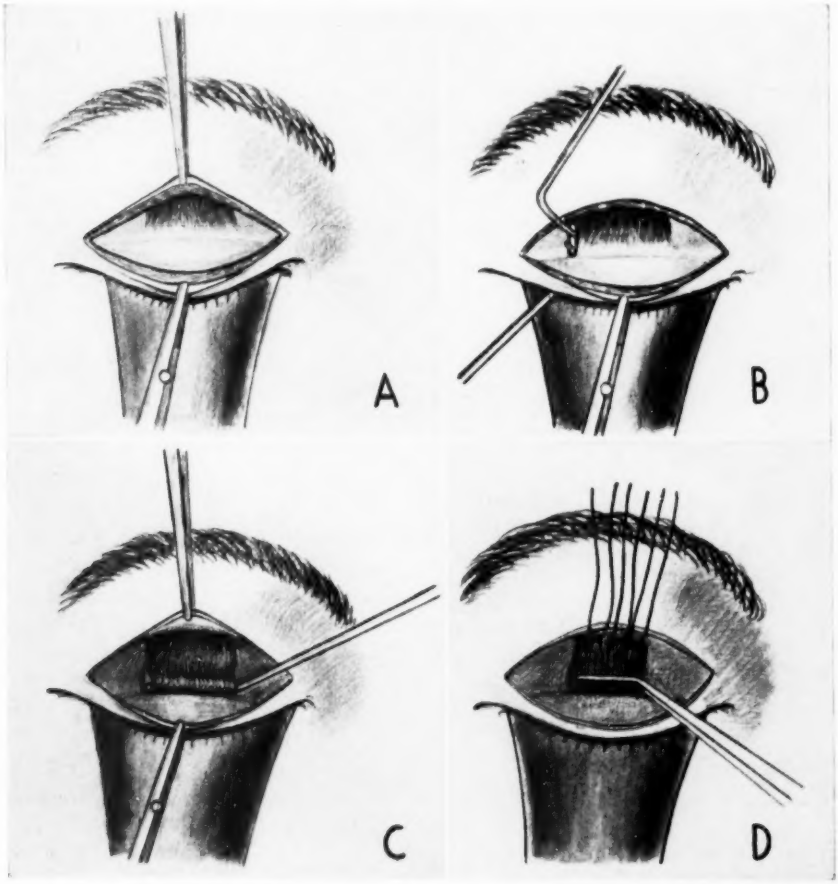

Fig. 6.—Advancement and resection of levator. (*A*) A horizontal incision is made through the skin and orbicularis 9 mm. above the lid margin (shown too low in this diagram). Scissors dissection is carried down to the tarsal plate, which henceforth serves as the main landmark. (*B*) A small opening is made on each side of the muscle completely through the lid and conjunctiva. (*C*) A strabismus hook is passed under the muscle and conjunctiva. (*D*) Three 4-0 mild chromic catgut lock sutures are placed through the entire muscle thickness but not through the conjunctiva. A Prince forceps is applied, and about 1 cm. of muscle is excised from the tarsus to just below the sutures.

The stay sutures are next pulled through the bits of rubber catheter used as buttons until the lid is raised to exactly the right height and the proper marginal curve is obtained. The rubber

holds the sutures tightly enough so that the three sutures will remain tight temporarily without being tied, and the height and curve of the lid can be minutely adjusted and readjusted before the sutures are finally tied (Fig. 7*D*).

A Frost suture is inserted in the margin of the lower lid and anchored over adhesive tape on the forehead to pull the lower lid almost up to the upper lid margin. Ointment is instilled in the eye. Merbromin (Mercurochrome) or a similar squeous antiseptic is applied copiously to the skin and stay sutures and a dry gauze pad applied. For extra protection from evaporation, a piece of Cellophane is applied over the gauze pad for the first two days. The other eye is also covered for the first two days. Penicillin is administered daily for four days, at which time the patient is usually allowed to go home.

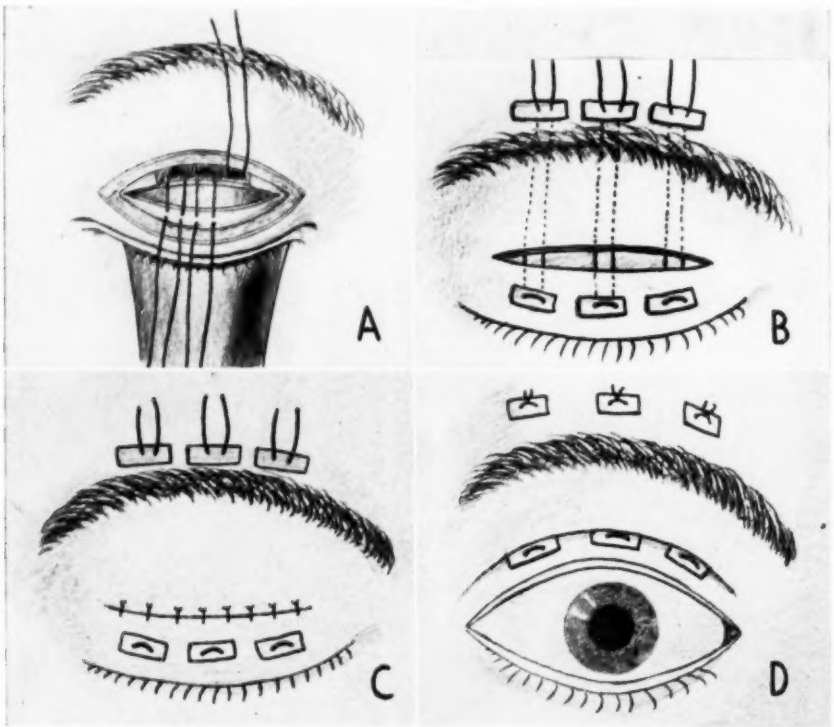

Fig. 7.—(*A*) The ends of the muscle sutures are carried down into the tarsus and tied to complete the advancement. No tarsus is resected. (*B*) Stay sutures of 5-0 silk are inserted through bits of rubber catheter from 3 mm. above the eyelashes to 3 mm. above the eyebrows. They pass just under the skin and the orbicularis. (*C*) The skin incision is closed with about eight sutures of 5-0 and 6-0 silk. Two of these sutures are deeply placed to include some fibers of the advanced levator muscle. (*D*) The stay sutures are drawn up through the rubber plates. After all three sutures have been adjusted to correct tightness, the knots are tied. The lower lid is pulled up later with a Frost suture to protect the cornea.

It should be emphasized here that any type of suture coming out on the lid margin, rather than just in front of the lid margin, is clinically unsound. If such an intramarginal suture is under moderate tension, troublesome cicatricial entropion may result. Sutures just in front of the line of lashes, however, prevent any tendency for this entropion to occur.

There is usually marked edema of the lower part of the upper lid for a week following this procedure. If the edema remains intense, it is best to take out the stay sutures in four days so

that the pressure on the lower rubber buttons will not leave any marks on the skin. The upper buttons are saturated with a skin antiseptic, and the sutures are cut just under the upper buttons. The lower buttons, with the sutures attached, are then pulled out easily.

Results.—In a series of approximately 70 cases in which this operation has been done since 1934, the results have been extremely satisfying. The horizontal lid scar

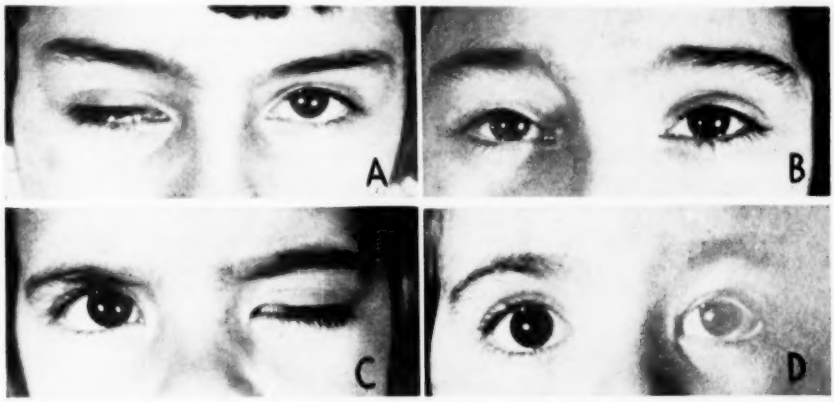

Fig. 8.—*A*, marked ptosis with slight levator action; *B*, two years after advancement and resection of levator by external route in patient shown in *A*; *C*, marked ptosis with slight levator action; *D*, appearance of patient shown in *C* one year after levator resection.

Fig. 9.—*A*, typical case five days after advancement and resection of levator, with stay sutures still in place. *B*, another case, two years after bilateral levator resection.

is invariably unnoticeable. There was no case of infection or of entropion, ectropion, or abnormal lid arching. In almost all cases there were good to excellent cosmetic results and lid motion. This procedure, of course, leads to shortening of the conjunctiva in the upper fornix, but clinically this seems to make no difference. In many cases, in fact, inspection of the upper fornix later fails to reveal observable shortening.

Between 1934 and 1938, the technique used was that described above except that no stay sutures were inserted, nor was the Frost suture [11] used afterward. A single stay suture centrally placed was used during the next few years. This had to be removed in three or four days to prevent arching in the center of the lid. In recent years, three sutures have been used routinely, and their use has sharply increased the percentage of completely adequate corrections.

Since this procedure restores a normally wide palpebral aperture even in a case of very marked ptosis, a minor complication frequently found later in extreme cases is a redundant fold of lid skin. In a few cases of very pronounced ptosis in old people, in which the lid skin was stretched and nonelastic, this redundant skin fold was actually enough to touch and slightly depress the lashes of the upper lid. In approximately 10 of the 70 cases it was considered advisable to excise an elliptical piece of skin along the line of the old incision later in order to get rid of this extra fold.

The original procedure (without use of stay sutures) has become widely used in the New England area during the last 15 years, and at present is much more popular there than the conjunctival-route technique. It was adopted by Johnson [12] with one excellent variation. Before suturing the skin, he used sutures through each skin edge and tarsus in an attempt to create a natural-looking skin fold.

> The silk suture is passed through the lower skin edge, then into the tarsus (through the previously advanced levator . . .) at a point high enough to put the lower skin flap on a slight stretch, then out through the upper skin edge. The suture is tied just tight enough to approximate the skin edges well. If it is tied too tightly, the resulting lid fold tends to be unnaturally deep. Three of these sutures are sufficient in the usual skin incision and the remaining gaps can be closed by ordinary interrupted skin sutures.

I have not made use of this modification myself, since the stay sutures described above serve the same purpose and also provide effective elevation of the lid until the levator is satisfactorily healed. Furthermore, I place the skin incision well above the upper tarsal border; so the Johnson sutures would not be effective. The higher incision is preferable, since, even if a scar should be faintly discernible, it is covered by the normal skin fold when the eye is open.

SUMMARY

In cases of marked ptosis with complete levator paralysis and normal frontalis action, suspension of the lid to the frontalis muscle with a single 2-0 white silk suture is simple and satisfactory and is considered the operation of choice.

When there is even very slight levator action, resection and advancement of the levator is to be preferred. A simple and very effective technique is outlined for resection of the levator via the external route.

After resection and advancement of the levator, the use of three temporary stay sutures from just above the lid margin to the eyebrow is extremely helpful in obtaining an adequately wide palpebral aperture.

9 Central St.

11. Frost, A. D.: Supporting Suture in Ptosis Operations, Am. J. Ophth. **17**:633 (July) 1934.
12. Johnson, C. D.: Ptosis Surgery, Am. J. Ophth. **34**:108 (Jan.) 1952.

EXPERIMENTAL RADIATION CATARACT

III. Further Experimental Studies on X-Ray and Neutron Irradiation of the Lens

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IN PREVIOUS reports of this series [1] describing the ocular events in rabbit eyes following exposure to x-rays and neutrons, abnormalities in the lenses were unexpectedly found at the lowest dose levels used (250 r for x-rays and 1.0×10^9 neutrons/cm.^{2}). It is the purpose of this communication to report the effects on the lenses of rabbits of a single exposure to x-rays and to neutrons at lower dose levels and to present a calculation of the energy released in the lens with exposure to comparable cataractogenic doses of x-rays and of neutrons.

At the outset the difficulties inherent in determining a threshold level may be mentioned. Thus, if no opacification of the lens occurs with a given amount of radiation, the objection may legitimately be raised that the observations have not been followed over a sufficiently long period; it is well known that the lower the dose the longer the latent period. None of the observations here reported have been made for periods of less than one and a half years, which is approximately one-third the life span of the animal; nevertheless, that possible objection still holds.

Another, and perhaps more serious, source of uncertainty encountered in determining threshold levels is the decision as to where the normal variation leaves off and the significantly abnormal begins. A cataract has always been by definition an abnormal opacity of the lens, but it is well known that punctate dots simulating the early opacities in the lens following irradiation are occasionally found in routine examination of eyes that have not received any radiation and that are otherwise

Work done under the auspices of the United States Atomic Energy Commission.

From the Los Alamos Medical Center, the Los Alamos Scientific Laboratory of the University of California, Los Alamos, N. Mex., and the Howe Laboratory of Ophthalmology, Harvard Medical School (Dr. Cogan and Dr. Donaldson); Los Alamos Medical Center and the Los Alamos Scientific Laboratory of the University of California (Dr. Goff), and Los Alamos Scientific Laboratory of the University of California (Dr. Graves).

1. (*a*) Cogan, D. G., and Donaldson, D. D.: Experimental Radiation Cataracts: I. Cataracts in the Rabbit Following Single X-Ray Exposure, A. M. A. Arch. Ophth. **45**:508-522 (May) 1951. (*b*) Cogan, D. G.; Goff, J. L., and Graves, E.: Experimental Radiation Cataract: II. Cataract in the Rabbit Following Single Exposure to Fast Neutrons, ibid. **47**:584-592 (May) 1952.

normal. These "normal variations" that occur in the rabbit eye have been carefully described by Poppe.[2] Since they consist of granular dots situated along the posterior suture line, they cannot be differentiated objectively from the minimal changes occurring after irradiation. To circumvent this difficulty, all eyes were examined carefully prior to irradiation, and an effect was ascribed to radiation only if there was a significant increase in the preexisting opacities. But this is not sufficient, since the opacities in normal eyes are often so slight that they can be seen on one occasion and overlooked on another. Thus, if they had not been seen on an examination prior to irradiation and had been seen on a subsequent examination, they might well have given rise to the erroneous impression of a radiation effect. A more reliable differentiation of the significant radiation effects at threshold level might be expected from a comparison of the number of abnormalities found in a series of irradiated animals with a series of nonirradiated controls. Accordingly, results were considered positive only when the opacities were found more frequently and more persistently in a group of irradiated than in a group of nonirradiated animals.

EFFECTS OF RELATIVELY LOW DOSAGE

X-Rays.—It was previously established that exposures to an x-ray dose of 250 r (1.2 mev) was sufficient to induce granular opacities, preferentially along the posterior suture line of the rabbit lens. One of the rabbits so treated has been followed for a total of 760 days and has shown no progress of the opacity over that noted a few weeks after its first appearance.

The present experiment was intended to repeat the exposure at this and at lower dose levels.

Technique: Pigmented rabbits were exposed to x-rays (1.2 mev) in dose ranges of 75, 150, and 250 r. One eye only of each animal was irradiated, the other eye serving as a control. Ophthalmoscopic examination of the eyes was carried out approximately every 50 days. The observation period following irradiation was 18 months.

Controls: Periodic observations were made on seven unirradiated rabbits in such a way that the examiner did not know at the time whether he was examining an irradiated or an unirradiated animal. In three of the eyes, dots were seen in the posterior capsular region on a single observation that had not been seen on the preliminary examination. In none were changes found that the examiner thought were unequivocally radiation-induced opacities.

Test Eyes: Observations on these eyes are summarized in the following tabulation.

Dose, r (1.2 Mev)	No. of Eyes	Occurrence of Opacities		
		Definitely Positive	Borderline	Negative
250	5*	2	3	0
150	24	8	14	2
75	13	2	7	4
Controls	7	0	3	4

* This group does not include those irradiated with 250 r and reported in the previous study.

Especial attention was directed to the question of progression of the opacities throughout the 18-month observation period. All the opacities in the 250-r group progressed to a certain stage within the first few months and then remained station-

2. Poppe, E.: Experimental Investigations of the Effects of Roentgen-Rays on the Epithelium of the Crystalline Lens, Acta radiol. **23**:354-367, 1942.

ary for the rest of the period. Of the opacities in the 150-r group, approximately one-half remained stationary and one-half regressed, some to the point of complete disappearance of the opacity. The course of the opacities in the 75-r group was inconclusive, owing to the small number of definitely positive cases.

Neutrons.—In the previously reported study it was noted that in rabbits exposed to as low a dose as 1×10^9 neutrons/cm.^{2} (of degraded fission neutron energy [3]) lens changes ascribable to radiation developed. Of this series, eight rabbits which had received doses ranging from 4×10^9 to 1×10^9/cm.^{2} have been followed further, to a total of 28 months. The opacities have remained stationary as punctate dots, situated preferentially along the posterior suture line in four eyes, while they have shown slight evidence of increase, but never amounting to more than punctate dots along the posterior suture line, in the other four.

For the present study, dose levels were selected which would overlap the above but extend much further down in the low-dose range.

Technique: Thirty rabbits were exposed to neutrons of degraded fission energy according to the method previously described.[1b] Dosage levels of exposure were selected to extend from 4×10^9 to 1×10^7 neutrons/cm.^{2} and one eye only of each animal received the measured amount of radiation. The opposite eye of each animal received an undetermined amount of radiation and will not be considered further. Groups of two to three rabbits were exposed to serial doses distributed so that each group received approximately one-half the dose of the preceding group. The eyes were examined ophthalmoscopically about once a month for 18 months.

Controls: Fourteen rabbits which received no radiation were examined periodically in the same manner as the exposed rabbits. These 14 included 8 rabbits which were found to have one or more punctate dots in the region of their posterior capsule and were, therefore, excluded from the radiation group. In only one of these eight were the dots found on subsequent examination. Of the other six, nonirradiated rabbits, dots in the region of the posterior capsule were found transiently in two rabbits.

Test Eyes: With one exception, lens opacities that were greater in extent and more persistently present than in the normal were found in all the rabbits which received the neutron irradiation. The only exception was one of the three rabbits whose eyes were exposed to 1×10^7 neutrons/cm.^{2}, that is, the minimal dose. The amount of opacification varied to some extent with the amount of radiation, but in no case did it consist of more than punctate granular dots along the posterior suture lines.

It thus appears that significant opacities in the posterior capsular region were found in rabbit eyes that were irradiated with neutrons in doses as low as 1.0×10^7 neutrons/cm.^{2} These opacities, however, were slight in doses less than 1×10^9 and were not individually greater than one sees as normal variants; nor did they appear to be progressive over an observation period of 20 months after they had made their first appearance.

Summary and Comment of Low Dosage Effects.—The lens opacities with low-dosage radiation (x-rays or neutrons) of rabbit eyes consist of granular dots arranged preferentially along the posterior suture line. Optically they appear to be

3. Since the source was the Fast Reactor, the neutron energy was that of a modified fission spectrum with a maximal intensity at 300 kev.

exaggerations of what is occasionally seen in the normal eye. In studies elsewhere reported [4] they have been found microscopically to consist of aberrant cells that have migrated from the equator. The opacities produced by low-dosage radiation reach a plateau of density and then may remain stationary for at least several months or may be regressive during the 18-month observation period.

The concept of an absolute threshold level for radiation cataracts appears to be negated by these observations; the lower the dose the less conspicuous are the changes observed until a point is reached where the abnormalities cannot be differentiated from the normal. The end-point is determined by the astuteness of the observer and by the limitations in the means used for examination. In the present study abnormalities attributable to radiation could be found with 75 r of x-radiation and 1.0×10^2 neutrons/cm.^{2} It is reasonably certain that with other means of examination, permitting greater resolution, significant effects could be detected with even less radiation. Such further refinement would have no practical consequence, however, as the present observations are sufficient to indicate that the changes in the lens from radiation do not have a critical threshold.

It becomes necessary, therefore, to specify what is meant by a radiation cataract. To define it simply as an opacity of the lens resulting from irradiation is unsatisfactory from the practical point of view, since the transition from physiologic to pathologic is ill-defined and dependent on arbitrary methods of examination. On the other hand, to consider that a cataract exists only when there is complete opacification of the lens is equally objectionable in that it ignores the obviously significant intermediate stages. Finally, the criterion of progression whereby a cataract could be called such only in retrospect is likewise untenable. Actually, lens opacities are of significance only when they result in measurable reduction of vision. In lay parlance, cataract is synonymous with this, and it would probably be least confusing to confine the term cataract to those opacities which have resulted in reduction of vision.

By comparison with lens opacities in human beings those noted in the foregoing experiments would not be expected to induce any measurable reduction in vision. In accordance with our strictly practical definition, they would not be called cataracts. The minimal amount of radiation which produced opacities that might be expected to reduce vision, had they occurred in human beings, was approximately 500 r for x-rays of 1.2-mev energy and approximately 8.4×10^9 for neutrons of 14-mev energy and 3.2×10^{10} for neutrons of degraded fission energy.[1b] This threshold, unfortunately, involves a matter of personal opinion as to what might impair vision but, nevertheless, seems the best approximation to a threshold according to our arbitrary definition of cataract. We shall use it in our subsequent reference to the "cataractogenic dose."

Granted that the foregoing level establishes an equivalence for the cataractogenic threshold, the equivalence does not appear to hold for lower levels. Thus, x-ray doses slightly in excess of one-tenth the cataractogenic dose produce detectable lens opacities in only a minority of the cases, while neutron doses of one two-hundredth the cataractogenic dose induce definite opacities in practically all cases. This, together with evidence on ionization equivalence to be presented, suggests an inherent difference in the x-ray and the neutron effects on the lens.

4. Cogan, D. G.; Donaldson, D. D., and Reese, A. B.: Clinical and Pathological Characteristics of Radiation Cataract, A. M. A. Arch. Ophth. **47**:55-70, (Jan.) 1952.

ENERGY RELEASED IN THE TISSUES AT CATARACTOGENIC DOSE LEVELS

Comparable cataractogenic levels for x-rays and neutrons having been decided on, it is of some moment to perform a calculation of the amount of ion pair production or energy released by each in the lens. Only on some such basis can one obtain a common denominator for assessing the relative cataractogenic properties of x-rays and neutrons. The selection of 500 r for x-rays (1.2 mev) and 8×10^9 for 14-mev neutrons and 3×10^{10} for Fast Reactor neutrons was based primarily on the degree of opacity. Equivalent cataractogenic properties are also suggested by the fact that these amounts of radiation produced an initial opacity beginning at approximately the same time (100 days).

The constituents of the tissue other than water make a negligible contribution to the energy release. Furthermore, consideration of the neutron cross sections and angular distribution of scattering for 14-mev neutrons leads to the conclusion that only the hydrogen in the medium need be considered for this calculation.

Since the range of 10-mev protons in tissue of 1 gm. per cubic centimeter is 1.2 mm.[5] and since the lens epithelium is approximately 2 mm. beneath the surface of the cornea, any possible surface effect may be ignored. Since the average energy loss per collision with a hydrogen atom is one-half the neutron energy, and the cross section for collision is 0.675×10^{-24} cm.^{2}, one obtains for the energy released to proton recoils by a flux of one 14-mev neutron per square centimeter, a value of 0.31 mev/per cubic centimeter in tissue of density of 1 gm./per cubic centimeter. The attenuation of the neutron beam by passing through 2 mm. of cornea and aqueous humor is only 2% and is neglected.

The calculation of this quantity for Fast Reactor neutrons follows the same course. However, since the neutrons are not monoenergetic, an integration must be performed. This has led to the conclusion that the energy released by Fast Reactor neutrons equals 0.11 mev/neut/cm.^{2}/cc.

These figures are used for determination of ionization in the following tabulation.

Radiation	Mev/Cc./Unit Flux	Equivalent Ergs/Cc./Unit (Mev $\times$ 1.6 $\times$ 10^{-6})	Cataracto-genic Dose	Equivalent Energy Released (Ergs/Cc.)
Neutrons (14 mev)	0.31 mev/neut/cm.^{2}/cc.	0.50×10^{-6}/neut/cm.^{2}	8.4×10^9/neut/cm.^{2}	4.2×10^3
Neutrons (fission)	0.11 mev/neut/cm.^{2}/cc.	0.18×10^{-6}/neut/cm.^{2}	3.2×10^{10}/neut/cm.^{2}	5.4×10^3
X-rays (1.2 mev)		93.1/r	500 r	46.5×10^3

It thus appears that the cataractogenic properties of neutrons used in the present experiments exceed those of x-rays by a factor of 10 when comparison is based on the relative amounts of tissue ionization. The cataractogenic properties of fission neutrons (with a maximum energy at 0.3 mev) and of high-energy neutrons (14 mev) show no significant differences when compared on the basis of tissue ionization.

CONCLUSIONS

Lens changes resulting from irradiation do not have a critical dose level. The lower the dose the less apparent are the changes, with an end-point depending chiefly on the method of examination. The term cataract is arbitrarily defined as a

5. Lea, D. E.: Actions of Radiations on Living Cells, New York, The Macmillan Company, 1947.

lens opacity that would be expected to result in some impairment of vision if it were to be present in the human lens. This results in the rabbit lens with an irradiation of the following types and amounts: x-rays, 500 r (1.2 mev); neutrons, 8.4×10^9 particles/cm.^{2} (14 mev), or 3.2×10^{10} particles/cm.^{2} (fission energy). With decreasing dosage the effects of irradiation of the lens decrease less rapidly with neutrons than with x-rays.

The energy released in the lens at the cataractogenic level, expressed as ergs per cubic centimeter, is 46.5×10^3 in the case of x-rays (1.2 mev) and 4.2×10^3 and 5.4×10^3 in the case of neutrons of 14 mev and fission energy, respectively. Thus, although the energy released is of the same order of magnitude at the cataractogenic level in the case of the neutrons of two widely different energies, it is less by a factor of 10 than in the case of x-rays. With equivalent ionization in tissue, neutrons are much more productive of cataract than are x-rays.

Lens opacities in the rabbit resulting from either 250 r (1.2 mev) or 1×10^9 neutrons/cm.^{2} (0.3 mev) or less characteristically reached a plateau of density and then either remained stationary or regressed.

RELATION OF OCULAR DOMINANCE, HANDEDNESS, AND THE CONTROLLING EYE IN BINOCULAR VISION

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AND
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TWO PAPERS published in 1938 marked the inception of this investigation. One,[1] by us, dealt with visual handicaps and reading difficulties. We mentioned that a relation between crossed dominance and reading disability seemed to exist but needed further investigation. The other,[2] by Walter Fink, summarized and presented for the special consideration of ophthalmologists the existing knowledge of ocular dominance and crossed dominance. He began his investigation convinced that the solution of any problems arising from crossed dominance lay in the field of psychological research; he reached the conclusion that the problem most probably could, and would, be solved by ophthalmologists, and he asked for continued diligent research in this field.

For those ophthalmologists to whom it is new, the problem is here briefly stated. Among the children of normal intelligence who meet difficulty in learning to read is a group with a characteristic pattern. It begins in early childhood with the slow development of motor coordination, often accompanied by speech hesitations or frank stammering. At school age the children show poor visual imagery and memory, and reversals in reading and writing patterns, sometimes including complete mirror writing. Very poor reading and spelling are the outstanding difficulties. Nervous fatigue accentuates the problem. In more mature life the combined appearance of ocular discomfort, nervous disorganization, and disruption of established reading habits suggests a similar pattern of later origin.[3]

The connection of this chain of difficulties with crossed dominance has long been noted. For those to whom the problem is new, crossed dominance refers to the fact that the dominant (sighting) eye is on the side of the body opposite the preferred hand. But exhaustive surveys have failed to prove this a consistent link. Some children with crossed dominance have no such difficulties; some children with corresponding dominance exhibit the entire chain. The most complete survey is that of

1. Berner, G. E., and Berner, D. E.: Reading Difficulties in Children, Arch. Ophth. **20**:829-838 (Nov.) 1938.

2. Fink, W. H.: The Dominant Eye: Its Clinical Significance, Arch. Ophth. **19**:555-582 (April) 1938.

3. Those who feel that a too comprehensive chain of symptoms has been suggested are referred to an article by J. Roswell Gallagher (Can't Spell, Can't Read, Atlantic **181**:35-39 [June] 1948). The entire group of symptoms is there described by a physician-educator as part and parcel of a single problem.

Johnston,[4] who found no correlation outside the operation of chance between anomalies of lateral dominance and reading disability in the group of children which he studied.

Fink [2] suggested, and we were then investigating, the probability that the source of this disability might lie in established patterns of binocular vision. Selzer [5] stated that he believed that "lack of integration resulting from lack of visual fusion will eventually prove to be the missing link of the situation." This assumption could easily be discarded, as these children proved to have good fusion and binocular stereoscopic vision.

When binocular vision has developed, there remains one visual act which is essentially monocular. This is the act of sighting.[6] The sighting eye is called the dominant eye. It is established in early life and is stable.

As binocular vision develops, it becomes habitual to use two eyes as a unit for visual perception. But within the pattern of binocular vision there is rivalry between the two eyes, and one eye controls binocular perception. This eye we have called "the controlling eye." The other eye plays an assisting, rather than an equal, role. The eye which controls binocular perception is not necessarily the eye with which the person sights. The sighting, or dominant, eye is selected for an essentially monocular act; the controlling eye gains its mastery within the pattern of binocular vision. The dominant eye is stable from early life, but the controlling eye can be shifted, as the binocular pattern is easily influenced by changes in vision, or controlled by training.

When a person has binocular vision, his motor reactions, speech, reading, and writing are initiated by binocular images. Our investigations have led us to believe that when the controlling eye is on the side opposite that of the handedness, the motor initiation is poor and difficulties in speech, reading, and writing ensue. These difficulties can be relieved by shifting the control of the binocular pattern to the side of the handedness. Similar difficulties do not occur when the controlling eye is on the side of the handedness.

EXAMINATION, DIAGNOSIS, AND TREATMENT

The diagnosis of this condition and the direction of treatment are an ophthalmological problem. Educators cannot solve the difficulties encountered by the affected children without the aid of binocular vision examination, meticulous refractions, and supervision of the necessary occlusion or binocular vision training.

Children are referred to an ophthalmologist for consultation primarily for poor vision, for eyestrain caused by the use of eyes in learning, or for failure to learn, especially in reading and spelling, as well as others of their age and mental level. The examination of the last group should include questions on the development of

4. Johnston, P. W.: The Relation of Certain Anomalies of Vision and Lateral Dominance to Reading Disability, Monographs of the Society for Research in Child Development, Vol. 7, No. 2, Washington, D. C., National Research Council, 1942.

5. Selzer, C. A.: Lateral Dominance and Visual Fusion: Their Application to Difficulties in Reading, Writing, Spelling, and Speech, Harvard Monographs in Education, No. 12, Cambridge, Mass., Harvard University Press, 1933.

6. Walls, G. L.: Theory of Ocular Dominance, A. M. A. Arch. Ophth. **45**:387-415 (April) 1951.

muscular coordination, speech, and handedness. Notations of actual hand use should be made, including any attempted or accomplished change of handedness, and the occurrence of reversals in reading or writing ("saw" for "was," etc.) asked for.

The determination of ocular dominance by sighting tests is not necessary. It has been done in our series of cases for purposes of comparison, but it is unnecessary when a determination is made of the eye which controls the binocular vision. Examination of visual acuity, fundi, and muscle balance is routine. Examination of fusion, stereoscopic perception, and vergence powers follows. When the existence of binocular vision is accepted, we attempt to determine the controlling eye. In the Keystone Visual Skills tests, published by the Keystone View Company and usable in a Telebinocular, are two cards, DB2-D and DB3-D. These cards compare the relative performance of the eyes during the act of binocular vision. It will often happen that an eye with relatively less visual acuity, as measured monocularly on a Snellen chart, performs noticeably better in picking out the dots on binocular targets, indicating that there is a strong demand for this eye to lead the binocular vision pattern. Great care must be exercised that these cards are exposed at infinity and that accommodative impulses of the eyes have been relaxed. We do this by presenting several interesting and easily fused stereoscopic pictures before the exposure of the targets. Percentages are read as given in tables on the back of these cards, and the function tested is noted as binocular efficiency.

Keystone Tests of Binocular Skill are used to determine the controlling eye in the binocular pattern of reading. These are selections at different reading levels of matched paragraphs for reading with two eyes together, the right eye alone with the left eye open, and the left eye alone with the right eye open. They are presented at the clearest reading distance. The reading is timed for number of seconds and errors. When a child cannot read at all, near-point vision is used for binocular fusion of such targets as Wells's E. Suppression and poor quality of a part of the fused image indicate the eye with relatively lower binocular efficiency.

A diagnosis of the controlling eye in binocular vision is made upon the data gathered in these examinations. The noncontrolling eye may have relatively poor visual acuity with suspected refractive error. It may be a postamblyopic eye that has never gained excellent use even though binocular vision has been established. It may have the same visual acuity as the controlling eye but lag when tested in the binocular pattern. The noncontrolling eye may lag in the reading situation only; such children are less likely to give a history of preschool difficulty and have clearly defined difficulty with reading and spelling only. The diagnosis of hand-eye confusion is made when the eye which controls the binocular vision is on the side of the body opposite the hand used.

Treatment is directed toward measures which will establish the controlling eye in binocular vision on the side of the hand used. Refraction and the constant use of glasses may shift the binocular control. Occlusion, used as in the treatment of amblyopia, may be necessary, along with the use of glasses. Occlusion and limitation of all hand performances to one hand alone are the only treatment measures when refraction is normal. Treatment is continued until the controlling eye is established on the side of the handedness and remains in control after six weeks of unrestricted use of binocular vision.

ANALYSIS OF CASES

Over 600 children and adults have had their binocular vision patterns and hand use analyzed. Excluded from this analysis are all patients with high phorias, all patients with early disabilities whose records are incomplete, patients for whom treatment has been too recent to show results. Five hundred patients have been selected for this report.

The data are analyzed with reference to the dominant eye, the handedness, and the eye which controls the pattern of binocular vision. The inclusion of dominance is necessary in this first report in order that we may confirm the evidence already gathered from the literature that crossed dominance is not, of itself, the deciding factor in this disability. The weight of evidence from this study suggests that the deciding factor is noncorrespondence between the handedness and the controlling eye in binocular vision patterns. We have termed this condition "crossed control." The alternate state, in which the handedness and the eye which controls the patterns of binocular vision are on the same side, we have termed "corresponding control." The extremely brief summary of 500 cases relevant to our investigation follows. We have volunteered to have mimeographed a detailed discussion of the cases, with case reports and suggestions for cooperative treatment by ophthalmologists and educators. This analysis will be sent along with reprints of the present article to interested physicians, psychologists, and educators.

The 500 cases are divided for analysis into four main groups.

I.	**Patients with crossed control—all with difficulties in reading and spelling or in speech and allied visual motor patterns**	
	I A Crossed control along with crossed dominance	
	Right-hand, left-eye control (left eye dominant)	157
	Left-hand, right-eye control (right eye dominant)	23
	I B Crossed control, despite unilateral dominance	
	Right-hand, left-eye control (right eye dominant)	92
	Left-hand, right-eye control (left eye dominant)	12
II.	**Patients with corresponding control, having difficulties from another cause, or no difficulties**	
	II A Corresponding control, along with unilateral dominance	
	Right-hand, right-eye control (right eye dominant)	46
	Left-hand, left-eye control (left eye dominant)	21
	II B Corresponding control, despite crossed dominance	
	Right-hand, right-eye control (left eye dominant)	42
	Left-hand, left-eye control (right eye dominant)	12
III.	**Patients with ambidexterity**	
	III A With difficulties, solved by limitation to use of one hand, on side of controlling eye	37
	III B With difficulties, solved by limitation to use of one hand and development of corresponding control	21
	III C Without difficulties, analysis of binocular pattern	3
IV.	**Adults, with difficulties provoked by the disruption of an established pattern of corresponding control**	24

COMMENT

Of the 376 (75% of the 500) patients showing all or part of the chain of symptoms (Groups I, IIIA, IIIB, and IV), 23 (6%) either did not return or would not cooperate with what was an unfamiliar program. The remaining 353 (94%) cooperated until we had achieved a measurable shift of control, with marked improvement or complete relief of all their difficulties. The high incidence of these difficulties among children who have crossed dominance indicates why a relation has so long been sought between this type of reading difficulty and crossed dominance. But the matter resolves itself into the fact that the conditions which operate to produce crossed dominance can also operate to produce crossed control. They do not necessarily do so, and, on the contrary, crossed control can exist along with unilateral dominance.

When children are very young and ambidextrous, we are successful in directing that the handedness be developed on the side of the controlling eye. Other investigators, notably Claiborne [7] and several who have made personal reports to us, have been able to relieve stuttering by reversing the manual dexterity. They have not been able to explain this success, as the dexterity sometimes had to be established on the side opposite the dominant eye. This new concept of dexterity on the side of the binocular control is a logical explanation of their success.

When children are more mature and the hand use more developed, it is often necessary to accept the hand used for writing as unchangeable. If the controlling eye is on the opposite side, it must be reversed, and the hand use limited to the same side as the writing hand. This condition occurs most frequently in left-handed children taught to use the right hand. While this custom is deplorable, it is at least an enormous step forward to have found a method to relieve the difficulties it causes.

Analysis of Cases

	I A	I B	II A	II B	III A	III B	III C	IV
Sex								
Male	126	82	31	23	28	23	2	10
Female	54	22	37	30	9	8	1	14
Average age	7 yr. 8 mo.	8 yr. 2 mo.	8 yr. 5 mo. 2 adults	8 yr. 2 mo. 3 adults	7 yr. 4 mo.	7 yr. 2 mo.	30 yr	22 yr.
Notable reversals and/or speech difficulties	103	81	..	..	27	30	..	..
Treatment								
Glasses (constant) to change control	28	34	..	..	..	4	..	6
Glasses and occlusion to change control	55	27	..	..	..	6	..	4
Occlusion only to change control	83	37	..	..	..	18	..	5
Any restriction or change of handedness	..	..	..	..	37	31	..	9
Average time until first marked improvement	7 mo.	4 mo.	..	..	3 mo.	4 mo.	..	3 mo.

Among adults, the disruption of an established pattern of corresponding control precipitates some of this chain of difficulties. Wall's study mentions the finding of emmetropes who have higher acuity in the nondominant eye, without symptoms. When we have analyzed such patterns, we have found corresponding control. Disruptions occur exactly as in children. We see refractive changes which throw the burden of distant vision upon the side opposite that of established control, or which shift the reading control. Some few people revert to left-handed activities in adult life after long years of schooling and complete right-side control. Sometimes typists and others with copying activities are advised to place material to be copied on the side of the dominant eye. If a strong corresponding control exists on the side opposite that of dominance, this placing of material can cause serious discomfort. Relief in adult difficulties is effected as in the younger group. Refraction, training, limitation of ambidextrous use of hands, and placing of material all aim to establish (in adults more frequently to reestablish) corresponding control.

The remaining 124 patients (25%) have had examinations for various reasons. These included poor vision, eyestrain, suspicion of ocular difficulty, the recognition

7. Claiborne, J. H.: Stuttering Relieved by Reversal of Manual Dexterity, New York M. J. **105**:577, 1917.

of crossed dominance, or routine examinations requested despite lack of symptoms. Binocular vision examination revealed corresponding control, and symptoms could be relieved by treatment exclusive of an attempt to change control.

SUMMARY AND CONCLUSIONS

During the course of studies of binocular vision, we met evidence which led us to form the following hypothesis:

(*a*) When the controlling eye in binocular vision is on the side of the handedness, no chain of symptoms referable to eye-hand confusion is likely to occur.

(*b*) When the controlling eye in binocular vision is on the side opposite the handedness, some part or all of the chain of symptoms is likely to occur.

(*c*) When two hands are used, the stronger the relative control of one eye (if the controlling eye is on the side opposite the more commonly used hand) the more likely symptoms are to occur. Reversely, if the use of a second hand disrupts a well-established eye-hand pattern on the opposite side, symptoms are likely to occur.

Investigation of more than 500 patients with and without symptoms of reading difficulty, defects of speech, and allied visual-motor disorganization convinced us that this hypothesis operates beyond the operation of chance.

Treatment based on these concepts is a distinct adjunct to the successful handling of many cases which reach the ophthalmologist in consultation.

EXPERIMENTAL PRODUCTION OF RADIATION CATARACTS BY FAST NEUTRONS

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THE PRACTICAL problem of the accidental, and at times unavoidable, exposure of personnel to fast neutrons during the handling of fissionable material, as well as the possibility of more widespread exposure in time of war, stimulated this study. The objectives of these experiments were to determine the fast-neutron dose in dogs which after a single exposure would result in the development of lenticular cataracts and to determine whether a small neutron dose repeated at frequent intervals had a greater or less tendency to produce cataracts than a single larger dose. These studies have been in progress for three years, and the following report represents our findings during this preliminary period.

METHODS

Dogs anesthetized with pentobarbital were rigidly positioned with the left eye closest to a directional beam of neutrons derived from a collimated 16 mev external deuteron beam striking a beryllium target 8 ft. (240 cm.) from the cyclotron. The neutrons were filtered through 0.03 in. (0.76 mm.) of cadmium and 1.0 in. (25.4 mm.) of lead. This decreased the gamma-ray exposure to less than one-thousandth the neutron dose. These neutrons were approximately 6 to 8 mev. The cadmium, lead, and 8 in. of concrete block shielded the body of the animal. Because of the directional nature of the neutron exposure, the eye closest to the target received a much larger neutron exposure than did the body of the animal. The right eye, being farther from the target than the left eye, received a considerably smaller dose of radiation. This dose was determined at the time of exposure by 25-r and 100-r Victoreen ionization chambers placed in line with the target and the eye of the exposed animal. The exposures are arbitrarily recorded as n values. Table 1 records the neutron intensity observed at various angles and distances from the beryllium target.

All animals were carefully examined with the ophthalmoscope and slit-lamp microscope prior to exposure and at regular intervals thereafter. Six groups of dogs of varying ages were exposed, and the development of cataracts was followed for two years. Although, as indicated later, many animals in this series had a periorbital inflammatory reaction after exposure, except for transient mild anemia and leucopenia, no systemic effects were noted. It should be recognized that the shielding of the body of the animal kept to a minimum the total body irradiation.

OBSERVATIONS

GROUP 1.—This group was composed of 10 adult dogs approximately 1 year of age. Clinical observation of these 10 animals for 24 months after a single eye

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From the Addison H. Gibson Laboratory and the Sarah Mellon Scaife Radiation Laboratory of the University of Pittsburgh School of Medicine.

exposure of 60 to 150 N failed to reveal any change in the lens of either eye. The right eyes of these dogs, which had received approximately 60.0 N two years previously, revealed no significant microscopic abnormality.

Group 2.—This group consisted of four puppies from the same litter, 82 days old at the time of exposure. The left eye of each dog received a dose of 150 N, and the right eye, 81.5 to 86.0 N. After three to eight weeks lace-like opacities developed in the lens of the left eye, with definite vacuolation. In two of the animals small vacuoles developed in the lens of the right eye, but no other changes were noted in this eye. After 10 to 12 weeks these eyes began to clear, and at 5 months no evidence of radiation damage to the lens or other ocular structure could be detected. Both eyes were clear in all these animals at the time of report, two years after exposure.

Group 3.—Three puppies from one litter 6 months of age and two puppies 5 months of age received 150 N to the left eye and 68.8 N to the right eye. These dogs were almost full-grown at the time of exposure and did not manifest any change in the lens during the first 11 weeks after exposure. Subsequent observation at irregular intervals over a period of two years failed to reveal any evidence of the development of cataract.

Table 1.—*Neutron Intensity from Deuterons on Beryllium Target*

Distance from Target, In.	N/μa/Min.	Angle from Center of Target	N/μa/Min. at 8 In.
3	66.0	0°	9.3
6	17.5	15°	7.2
8	9.25	30°	4.0
12	4.5	45°	2.7
16	2.25	60°	2.0
20	1.60	75°	1.3

Group 4.—Five puppies from a single litter aged 33 days received a single exposure of 150 N to the left eye and 60 N to the right eye. In these animals some vacuolation developed in the lens of the left eye after three weeks of observation; however, six weeks after exposure the entire litter died of a laboratory infection.

Group 5.—This group consisted of four litter mates 11 months old who received a single massive dose of 1,500 N to the left eye and 900 N to the right eye. In these four dogs, after two to three weeks, vacuolation developed in both lenses, with progressive opacification in the left eye. In four months the lesions had progressed to necrosis of the entire orbit, and the dogs were killed. At this time, four months after exposure, the left eye was completely destroyed, and there had been erosion of the bony orbit about the eye. Three of the four dogs had definite cataracts visible in the right eye. In one dog the vacuolation initially appearing in the right eye had not appeared to progress, although the destruction of the orbit in the left eye was complete.

Group 6.—This group consisted of five dogs approximately 3 years of age. In each instance the left eye received a single dose of 1,500 N; the right eye, a dose of 810 to 900 N. Definite cataractous changes developed promptly in the left

eye of only one animal. In the other animals there was prompt appearance of vacuolation in the left eye, but this did not proceed to cataract formation. In every instance the left eye became depilated, tender, and edematous, and this condition proceeded in three months to complete necrosis of the bony orbit of the eye with destruction of the globe. In one dog both the right and the left eye became depilated after three weeks of exposure; the destruction of the left eye proceeded to extreme necrosis, and after three months the right eye exhibited typical cataract formation without necrosis. In all dogs the right lens showed vacuolation; in three of these cataract developed, but in two no cataract was evident at the time the dog was killed, 17 months after exposure.

Microscopic examination of the eyes of three dogs in this group two years after exposure to 810 N revealed the epithelium of the cornea to be absent, with the cornea completely covered by a thick layer of fibrinous exudate, continuous with the com-

TABLE 2.—*Cataract Formation Following Fast Neutron Exposure in Rabbits*

Rabbit No.	3 N/Wk. Total Body Irradiation, No. Wk.	Total Radiation Dosage, N	Post-Treatment Follow-Up Interval, Mo.	Comment
117	26	80.6	7	
118	17	52.7	4	
119	27	83.7	12	
120	26	80.6	7	
121	24	74.4	5	
122	26	80.6	8	No definite evidence of cataract on ophthalmoscopic or slit-lamp examination
123	24	74.4	5	
124	21	65.1	5	
125	26	80.6	9	
126	26	80.6	7	
127	22	68.2	5	
128	21	65.1	4	
129	26	80.6	12	
130	27	83.7	10	
131	27	83.7	7	
132	27	83.7	12	
827	Single collimated dose of 50 N to right eye, 42 N to left		5	
829	Single collimated dose of 40 N to right eye, 33 N to left		3	Definite opacities on posterior lens capsule
830	Single collimated dose of 100 N to right eye, 82 N to left		2	

pletely necrotic superficial corneal layers. There were a massive leucocytic infiltration of the corneal stroma and abscess formation in several places. The deeper corneal layers retained the normal lamellar structure, and Descemet's membrane was intact. The limbus and the anterior portion of the sclera were thickened and edematous. At the base of the iris a leucocytic infiltration extended into the angle of the anterior chamber. In the retina there was degeneration of the ganglion cells. The anterior epithelium of the lens was absent. Beneath the posterior capsule of the lens some vacuolation was contained in a layer of globular aberrant cells. There was evident degeneration of the lens fibers at the equator with degeneration of the nuclei. One section demonstrated liquefaction of the posterior cortex of the lens. The portion of the lacrimal gland included in the sections showed leucocytic infiltration and increase in fibrous tissue.

Study of the brains of the animals in Groups 5 and 6 are not complete, but atrophy of the frontal lobe on the side adjacent to the left orbit is grossly evident.

Additional Experiments.—Sixteen male albino rabbits received a total body exposure of approximately 3.1 N from a similar external neutron beam once a week for 17 to 27 weeks. These animals, with a total accumulated radiation dose of 52.7 to 83.7 N, were observed by ophthalmoscopic and slit-lamp examination for 4 to 12 months after cessation of exposure. During this period none of these animals presented definite evidence of lenticular cataract (Table 2).

Three rabbits in this series received a single collimated neutron dose of from 33 to 100 N, similar to the exposures of the dogs described above. The eyes of these animals all manifested definite opacities in the posterior lens capsule in the two- to five-month observation period after cessation of exposure.

COMMENT

It is well known that the ionization chamber technique used for quantitating this type of neutron exposure [1] is far from satisfactory as an absolute measurement of neutron flux. This deficiency has been rectified in part, however, by the recent development of improved apparatus for the detection of these relatively fast neutrons and separation of the gamma component.[2] Until the experiments here reported, using 6- to 8-mev neutrons, are repeated with more accurate dosimetry, any attempt to calculate the exposure in reps is very likely to permit misleading conclusions. However, as these animals were followed for two years after an exposure determined by the ionization chamber technique, it is felt that the information should be made generally available. Probably with more accurate dosimetry any discrepancies in the data available in the literature [3] on the cataractogenic dose for neutrons may be resolved.

SUMMARY

One exposure to a collimated beam of 6- to 8-mev neutrons of 60 to 150 N failed to produce clinically evident lenticular cataracts in dogs over a two-year period of observation. In puppies and young dogs some vacuolation of the lens may follow this dose of radiation, but this is not followed by cataract formation.

The administration of 810 to 900 N resulted in cataract formation in 60 to 75% of the eyes of adult dogs.

A dose of 1,500 N resulted in complete necrosis of the globe, orbit, and surrounding structures three to four months after exposure.

In 16 rabbits a total neutron whole-body radiation exposure of 52.7 to 83.7 N administered at weekly intervals in a dose of 3.1 N for 17 to 27 weeks failed to produce cataracts in a 4- to 12-month follow-up period after cessation of exposure.

A single collimated neutron dose of from 33 to 100 N produced definite cataracts in two to five months in the three rabbits exposed.

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1. Abelson, P.: Neutron Interactions with Tissue, prepared for the Division of Medical Sciences, National Research Council, 1950.

2. Hurst, G. S.; Ritchie, R. H., and Wilson, H. N.: A Count-Rate Method of Measuring Fast Neutron Tissue Dose, Rev. Scient. Instruments **22**:981, 1951.

3. Cogan, D. G.; Goff, J. L., and Graves, E.: Experimental Radiation Cataract: Cataract in the Rabbit Following a Single Exposure to Fast Neutrons, A. M. A. Arch. Ophth. **47**:584, 1952.

EFFECT OF HYALURONIDASE ON NEW VESSEL FORMATION IN THE CORNEA

An Experimental Study

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THE PRESENCE of hyaluronidase and its substrate in various tissues of the eye and their role in regulating the exchange of metabolites and water by influencing barriers existing at internal interfaces (Meyer,[1] 1947) have stimulated work on the eyes of men and animals within recent years.

If hyaluronidase is injected intraocularly in the rabbit, there results a prolonged inflammatory reaction (Pirie,[2] 1949; von Sallmann,[3] 1950; Linn and Ozment,[4] 1950). Its ability to increase the permeability of the lens capsule has been reported (Seifter and associates,[5] 1950). Hyaluronidase has no specific effect on the disappearance of red blood corpuscles from the vitreous of rabbits (von Sallmann[3]). It has been used to increase the effect of anesthetics injected retrobulbarly (Atkinson,[6] 1949). It has been instilled, with only temporary benefit but without severe reaction, into the anterior chamber of two patients with secondary glaucoma (Linn and Ozment,[4] 1950). Injections of hyaluronidase into the cornea have resulted in vascularization of that tissue (Meyer and Chaffee,[7] 1940). On the other hand, the inactivity of hyaluronidase as a spreading factor in the rabbit and ox corneas has called for reconsideration of the suggestion of Meyer and Chaffee that the observed corneal vascularization following the injection of hyaluronidase was due to the breakdown of the mucopolysaccharides (Woodin,[8] 1950).

1. Meyer, K.: The Biological Significance of Hyaluronic Acid and Hyaluronidase, Physiol. Rev. **27**:335, 1947.

2. Pirie, A.: Ox Vitreous Humour: Hyaluronic Acid Relationships, Brit. J. Ophth. **33**: 271, 1949.

3. von Sallmann, L.: Experimental Study on the Vitreous: Experiments on Disappearance of Red Blood Cells from the Vitreous, Arch. Ophth. **43**:638, 1950.

4. Linn, J. G., Jr., and Ozment, T. L.: Some Effects of Injection of Hyaluronidase into the Anterior Chamber, Am. J. Ophth. **33**:33, 1950.

5. Seifter, J.; Fitch, D. R.; Baeder, D. H., and Begany, A. J.: Action of Hyaluronidase and Steroids on Membrane Permeability, Am. J. M. Sc. **219**:346, 1950.

6. Atkinson, W. S.: Use of Hyaluronidase with Local Anesthesia in Ophthalmology: Preliminary Report, Arch. Ophth. **42**:628, 1949.

7. Meyer, K., and Chaffee, E.: The Mucopolysaccharide Acid of the Cornea and Its Enzymatic Hydrolysis, Am. J. Ophth. **23**:1320, 1940.

8. Woodin, A. M.: Hyaluronidase as a Spreading Factor in the Cornea, Brit. J. Ophth. **34**:375, 1950.

The following study was made to determine the influence of hyaluronidase on new-vessel formation in the cornea resulting from a simple traumatic lesion. It was hoped that the technique of assessment used might permit a definite conclusion.

METHOD

Standard lesions were made in both corneas of 23 rabbits, with an average weight of about 1,000 gm. The lesions were made by means of an electrocautery placed about 2.0 mm. from the limbus in the 12 o'clock meridian, according to a method previously described (Campbell and Michaelson,[9] 1948). The lesions were standardized by supplying a current of a fixed voltage for a fixed period. Each lesion was about 1.2 mm. in diameter and extended through about two-thirds of the cornea. Each lesion was renewed daily at the same site over a period of several days.

The right eye of each animal was treated with hyaluronidase or with Hyalase (Benger). The hyaluronidase was prepared from streptococcal culture and had a concentration of 300 mucin-clot prevention (M. C. P.) units per cubic centimeter. A hemolytic Streptococcus group A Lancefield, isolated from a sore throat, was grown for 18 hours in brain-heart infusion broth (Difco) at 37 C. After centrifugation at 8,000 rpm for half an hour, the supernatant fluid was removed aseptically and a pinch of streptomycin powder added to each 10 cc. of the supernatant fluid. Sterility was then assessed after incubation of fluid for 24 hours at 37 C., and when the fluid was sterile, the hyaluronidase content per cubic centimeter was estimated. Hyalase was supplied in the form of a sterile, freeze-dried powder of hyaluronidase contained in an ampule to which 1 cc. of sterile distilled water is added. Each cubic centimeter contains 1,000 Benger units of Hyalase. Messrs. Benger state that 1,000 Benger units is equivalent to at least 450 turbidity-reducing units (T. R. U.).

The hyaluronidase was used as follows:

1. One milliliter was injected once daily subconjunctivally at the 12 o'clock meridian in the right eyes of five animals until the end of the experiment for this group (length of experiment, three days).

2. One milliliter was injected twice daily subconjunctivally at the 12 o'clock meridian in the right eyes of three animals until the end of the experiment for this group (length of experiment, four days).

The Hyalase was used as follows:

1. One-half milliliter was injected twice daily subconjunctivally at the 12 o'clock meridian in the right eyes of four animals until the end of the experiment for this group (length of experiment, three days).

2. Two-tenths milliliter was injected twice daily subconjunctivally at the 12 o'clock meridian in the right eyes of 12 animals until the end of the experiment for this group (length of experiment, 13 days).

In all experiments the left eyes were used as controls. The left eyes received injections of the hyaluronidase preparations, inactivated by heating, in doses and at intervals corresponding to those used for the right eyes.

At the end of each experiment, the animal was given a lethal dose of Pro-Dorm, and immediately thereafter India ink was injected into the carotid arteries in order to demarcate the corneal vascularization resulting from the lesions. The ink was injected according to the method described by Campbell and Michaelson,[9] 1948. About 15 cc. was injected into each artery at a pressure of about 100 mm. Hg. After the injection the eyes were removed and placed in 10% formalin for one day. The appropriate pieces of cornea were then excised, cleared in glycerin, and mounted on slides. The extent of vascularization was measured by means of a micrometer eyepiece. Measurements were made of the distance of the ulcer from the limbus and of the base and height of the vascularized area from which its extent was estimated.

9. Campbell, F. W., and Michaelson, I. C.: Blood-Vessel Formation in the Cornea, Brit. J. Ophth. **33**:248, 1949.

RESULTS

First Hyaluronidase Experiment.—Daily dose, 300 M.C.P.; length of experiment, three days.

	Left Eye					Right Eye				
No. of Rabbit	Ulcer-Limbus Distance, Mm.	Height of Vascular Area, Mm.	Base of Vascular Area, Mm.	Size of Ulcer, Mm.	Area of Vascularization, Sq. Mm.	Ulcer-Limbus Distance, Mm.	Height of Vascular Area, Mm.	Base of Vascular Area, Mm.	Size of Ulcer, Mm.	Area of Vascularization, Sq. Mm.
1.....	1.9	0.6	5.0	1.1	1.5	2.0	0.6	5.0	1.1	1.5
2.....	1.5	1.0	5.7	1.0	2.8	2.1	0.6	5.0	1.1	1.5
3.....	2.3	0.5	4.6	1.0	1.1	2.3	0.5	4.5	1.0	1.1
4.....	2.0	0.5	5.0	1.1	1.2	1.9	0.8	6.5	1.1	2.5
5.....	2.5	0.5	5.0	1.0	1.2	1.9	0.6	6.5	1.0	1.9

Distance of the Ulcer from the Limbus: The mean for the control (left) eyes is 2.0 mm. (range, 1.5 to 2.5 mm); the mean for the treated (right) eyes is 2.0 mm. (range, 1.9 to 2.3 mm.).

As concerns the size of the ulcer and the ulcer-limbus distance, it may be accepted that the circumstances for the treated and for the untreated eyes were similar and that the areas of vascularization in the right and in the left eyes can be reasonably compared.

Areas of Vascularization: The mean for the untreated (left) eyes is 1.6 sq. mm. (range, 1.1 to 2.8 sq. mm.); the mean for the treated (right) eyes is 1.7 sq. mm. (range, 1.1 to 2.5 sq. mm.).

The difference of the means is not significant.

Second Hyaluronidase Experiment.—Daily dose, 600 M.C.P.; length of experiment, four days.

	Left Eye					Right Eye				
No. of Rabbit	Ulcer-Limbus Distance, Mm.	Height of Vascular Area, Mm.	Base of Vascular Area, Mm.	Size of Ulcer, Mm.	Area of Vascularization, Sq. Mm.	Ulcer-Limbus Distance, Mm.	Height of Vascular Area, Mm.	Base of Vascular Area, Mm.	Size of Ulcer, Mm.	Area of Vascularization, Sq. Mm.
6.....	1.7	1.0	7.5	1.1	3.7	1.8	0.8	7.5	1.3	3.0
7.....	2.0	1.0	5.5	1.1	2.7	1.8	1.0	7.5	1.0	3.7
8.....	1.5	1.1	8.5	1.3	4.6	2.0	1.3	7.5	1.4	4.8

Distance of Ulcer from Limbus: The mean for the untreated (left) eyes is 1.7 mm. (1.7, 2.0, 1.5 mm.); the mean for the treated (right) eyes is 1.8 mm. (1.8, 1.8, 2.0 mm.).

As concerns the size of the ulcer and the ulcer-limbus distance, the circumstances are sufficiently similar to permit comparison of the vascular triangles.

Areas of Vascularization: The mean for the untreated (left) eyes is 3.7 sq. mm. (2.7, 3.4, 4.6 sq. mm); the mean for the treated (right) eyes is 3.8 sq. mm. (3.0, 3.7, 4.8 sq. mm.).

The difference of the means is not significant.

First Hyalase Experiment.—Daily dose, 1,500 Benger units (675 T.R.U.); length of experiment, three days.

	Left Eye					Right Eye				
No. of Rabbit	Ulcer-Limbus Distance, Mm.	Height of Vascular Area, Mm.	Base of Vascular Area, Mm.	Size of Ulcer, Mm.	Area of Vascularization, Sq. Mm.	Ulcer-Limbus Distance, Mm.	Height of Vascular Area, Mm.	Base of Vascular Area, Mm.	Size of Ulcer, Mm.	Area of Vascularization, Sq. Mm.
9.....	2.0	0.6	7.0	1.2	2.1	1.9	0.6	7.5	1.3	2.3
10.....	1.9	1.0	7.0	1.3	3.5	2.0	0.8	7.0	1.2	2.8
11.....	2.0	0.8	5.0	1.3	2.0	2.3	0.4	6.0	1.0	1.2
12.....	2.0	1.0	7.5	1.0	3.7	1.9	0.8	7.5	1.3	3.0

Distance of Ulcer from Limbus: The mean distance for the untreated (left) eyes is 2.0 mm. (range, 1.9 to 2.0); the mean distance for the treated (right) eyes is 2.0 mm. (range, 1.9 to 2.3).

As concerns the size of the ulcer and the ulcer-limbus distance, the circumstances for the treated and the untreated eyes were similar.

Areas of Vascularization: The mean area for the untreated (left) eyes is 2.8 sq. mm. (range, 2.0 to 3.7 sq. mm.); the mean area for the treated (right) eyes is 2.3 sq. mm. (range, 1.2 to 3.0 sq. mm.).

There is no evidence that the Hyalase has increased the area of vascularization.

Second Hyalase Experiment.—Daily dose, 400 Benger units (180 T.R.U.); length of experiment, 13 days.

	Left Eye					Right Eye				
No. of Rabbit	Ulcer-Limbus Distance, Mm.	Height of Vascular Area, Mm.	Base of Vascular Area, Mm.	Size of Ulcer, Mm.	Area of Vascularization, Sq. Mm.	Ulcer-Limbus Distance, Mm.	Height of Vascular Area, Mm.	Base of Vascular Area, Mm.	Size of Ulcer, Mm.	Area of Vascularization, Sq. Mm.
13.....	2.0	2.5	7.5	1.1	9.4	2.5	2.3	7.5	1.3	8.6
14.....	2.0	3.0	10.0	1.3	15.0	2.5	3.3	11.0	1.3	18.2
15.....	2.5	3.3	9.7	1.3	15.7	2.8	3.0	9.5	1.3	14.3
16.....	2.5	3.3	7.8	1.0	12.9	2.8	2.8	7.5	1.0	10.5
17.....	2.5	2.0	7.5	1.4	7.5	2.1	2.5	7.6	1.2	9.5
18.....	2.0	2.0	6.6	1.0	6.6	2.4	2.1	7.5	1.1	7.9
19.....	2.5	2.6	8.8	1.1	11.4	2.3	2.6	10.0	1.1	13.0
20.....	2.5	3.0	8.8	1.3	13.2	2.5	3.3	10.0	1.2	16.5
21.....	2.0	2.3	8.0	1.3	9.2	2.2	2.5	10.0	1.3	12.5
22.....	2.5	3.0	8.8	1.2	13.2	2.5	3.0	88.5	1.2	12.8
23.....	2.5	2.6	8.0	1.4	10.4	2.5	2.6	8.8	1.3	11.4

Distance of Ulcer from Limbus: The mean distance for untreated (left) eyes is 2.3 ± 0.25 mm.; the mean distance in the treated (right) eyes is 2.5 ± 0.21 mm.

Size of Ulcer: The mean size for the untreated (left) eyes is 1.2 ± 0.14 mm.; the mean size for the treated (right) eyes is 1.2 ± 0.10 mm.

As concerns the size of the ulcer and ulcer-limbus distance, the circumstances in the treated and the untreated eyes were similar.

Areas of Vascularization: The mean area for the untreated (left) eyes is 10.9 ± 3.03 sq. mm.; the mean area for the treated (right) eyes is 11.9 ± 3.33 sq. mm.

The difference of the means is not significant.

COMMENT

The enzyme was from different sources and was given in various, but probably adequate, doses. The effect on vascularization was assessed at different intervals of time, varying from 3 to 13 days. The method of measurement of the vascularization appeared to be satisfactory. The results would appear to indicate that hyaluronidase when given subconjunctivally does not influence the spread of vessels into the cornea in the doses given and over the period exhibited. Short-period experiments (three to four days) were arranged because it was considered that the action, if any, of hyaluronidase on new-vessel growth would be at the onset of the vessel growth. The longer-period experiment 14 days) confirmed the findings. It is appreciated that hyaluronidase probably does not remain long at

the site of injection and that the ideal procedure is to supply it in a combination which would permit of slow absorption from a subconjunctival depot. Efforts are being made to find such a combination.

SUMMARY

A standard experimental lesion was placed in both corneas of rabbits and the subsequent vascularization observed after periods varying from 3 to 13 days. The extents of the areas of vascularization were measured microscopically after their injection with India ink.

The right eyes were treated daily with hyaluronidase obtained from a streptococcal culture, or with Hyalase, a commercial preparation produced by Benger. The ferment was injected subconjunctivally. The treatment was carried out up to 13 days.

The control (left) eyes received corresponding doses of the hyaluronidase or Hyalase inactivated by heating.

A comparison of the extents of the vascularization in the treated and in the control eyes indicates that the enzyme did not influence new-vessel growth into the cornea under the circumstances of the experiments.

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Ophthalmological Review

RADIATION CATARACT

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CYCLOTRON VICTIMS

DAMAGE to the lens arising from exposure to ionizing radiation was reported soon after the discovery of x-rays. Isolated cases of radiation cataract appeared among the early x-ray technicians and later among patients who had received radiation therapy to the head. These early cases were reported from time to time in the literature but occasioned scant interest outside ophthalmological circles.

Early in December, 1948, it became known that at least five nuclear physicists, of an average age of 31, had manifested incipient cataract. These scientists had a common history of exposure to radiation from the cyclotron, which was known to produce high fluxes of fast neutrons and hard gamma rays. Since it was probable from past experience that relatively high doses of gamma rays were needed to produce lens damage, the presumption was that fast neutrons might be the primary cause of cataract among these cyclotron workers. Accordingly, an ad hoc committee set up by the Medical Sciences Division of the National Research Council arranged to have questionnaires sent to most of the major laboratories in the country where comparable exposures might have occurred. This procedure uncovered a possible six additional cases of incipient cataract.

A meeting was held in Washington in January, 1949, under the auspices of the National Research Council and the United States Atomic Energy Commission, to discuss the problem. Some of the known cataract victims were present, and on the succeeding day 11 of these cyclotron scientists were examined in Baltimore at the Wilmer Ophthalmological Institute. Ten of them showed opacities of the lens, and 3 of them were grossly handicapped. The victims made every effort to estimate their exposures, but no great reliance could be placed on laboratory records several years old and on pocket dosimeters and film badges designed primarily to detect gamma rays. Abelson and Kruger reported the results of this initial survey. Durations of exposures ranged from 10 to 250 weeks, and estimates of the total neutron dose varied from 8 to 270 rep. It should be emphasized that these doses represented little more than educated guesses by physicists who were well qualified to estimate their exposures but who were handicapped by incomplete laboratory records and faulty instrumentation so far as neutron dosimetry was concerned.

From the Medical College of Virginia.

An abbreviated form of this review was given as a seminar to the Health Physics Division, Oak Ridge National Laboratory, in December, 1952. The Fourth Conference on Radiation Cataracts was held in Washington, D. C., Feb. 28, 1953, under the auspices of the National Research Council. Mimeographed copies of this review were prepared by the Committee on Radiation Cataracts and presented to participants at the opening of the Fourth Conference. Thus, the paper does not include, in detail, recent contributions made at the Fourth Conference, but every effort has been made to bring the subject matter up to date. Proceedings of the Fourth Conference on Radiation Cataracts should be available by midsummer, 1953, upon request from the Medical Sciences Division, National Research Council.

Since that time, four additional cases of radiation cataract have appeared among cyclotron workers in America, while Dollfus reported in May, 1950, a possible seven additional cases among workers on the cyclotron in Paris, France. Thus, a total of 21 scientists have, presumably, received damage to the lens from cyclotron irradiations. Friedenwald has presented the current ophthalmological status of these physicists.

ATOM BOMB VICTIMS

The Committee on Ophthalmology of the National Research Council sent a team to Japan during the summer of 1949 to investigate the incidence of radiation cataract among the survivors of the atomic explosions at Hiroshima and Nagasaki. This original survey, under the leadership of Cogan, found 10 victims with radiation cataract among the survivors. All were within 3,000 ft. (0.9 km.) of the hypocenter at the time of the explosion. Subsequent investigations have disclosed well over 100 persons with radiation cataract among the bomb survivors. The greatest distance from the hypocenter at which lens damage has been definitely established is about 3,600 ft. (1.97 km.). Estimates of the fast-neutron exposure at this distance from the so-called nominal bomb, of 20 KT, vary from 3 to 15 rep.; the corresponding gamma-ray exposure would be about 600 r.

Donaldson has reexamined 70 victims with radiation cataract among the Japanese whose clinical histories had been recorded by other ophthalmologists prior to his investigation, during the summer of 1951. Seventy per cent of these victims had suffered complete epilation following their exposures; 20 to 30% had suffered partial epilation. He found moderate regression of opacities in 2% of these patients, slight regression in 17%, no change in 36%, slight progression in 15%, moderate progression in 26%, and evidence of marked progression in 4%. This was six years after exposure to the bomb. Sinskey has reported on the current status of cataract victims in Japan; very few of them have suffered visual impairment as a result of exposure to the bomb.

ACCIDENTAL NUCLEAR-REACTION VICTIMS

Accidental nuclear reactions, which injured 10 scientists, occurred at the Los Alamos Scientific Laboratory in August, 1945, and May, 1946. In two of the survivors radiation cataracts have developed. Hempelmann, Lisco, and Hoffman have reported the case histories of 9 of these 10 victims. The radiations responsible for biological damage in these patients were primarily moderately fast neutrons and hard gamma rays emitted by a fast-fission process. The data presented in Table 1 are estimated from the report of Hempelmann and associates.

The neutron doses to the whole body, given in Column 3, were estimated from the Na^{24} content of the blood serum. While the absolute magnitude of the whole-body neutron dose may be in considerable error when calculated by this method, it does afford a rather accurate criterion of the relative doses received by the victims. Radioactive assay of the blood serum necessarily implies an estimate of the integrated dose to the whole body, and not the surface-tissue dose incident on the victims. Snyder's calculations by the Monte Carlo method show that fast neutrons incident on tissue are rapidly thermalized in their passage through the tissue. For example, neutrons of an average energy of 0.48 mev incident on tissue have a half-value-layer of roughly 4 cm. The fast-fission neutrons to which these scientists were

exposed probably were concentrated mainly in the energy range below 1 mev, so that the great majority of neutrons were thermalized and absorbed in passing through their bodies. From a consideration of the depth-dose curve in tissue for moderately fast neutrons, it seems probable that the surface-tissue dose was considerably larger than the whole-body dose; so the lens of the eye must have received a much larger dose of fast neutrons than would be indicated by the whole-body dose. The estimated doses to the eye given in Column 4 were obtained by multiplying the whole-body dose by a factor of 3, a conservative estimate under the circumstances applying here.

These estimates of the fast-neutron dose to the eye may be subject to errors of large magnitude, but they, at least, allow some conclusions to be drawn as to what constitutes a cataractogenic dose of fast neutrons for man. Victims 1 and 3 died of whole-body radiation exposure before lens anomalies could have been expected to develop. Victim 2 received an estimated dose of 6 rep of fast neutrons to the eye;

Data on Accidental Nuclear Reactions

Victim	Age, Yr.	Whole-Body Neutron Dose, Rep	Neutron Dose to Eye, Rep	Whole-Body Gamma Ray Dose, Roentgens	Nature of Accident
1	26	18	54	110	Touched assembly; died in 24 days
2	29	1.2	4	1	Twelve feet from assembly; lenses normal 4 yr. after exposure
3	32	74	222	114	Touched assembly; died in 9 days
4	34	15	45	26	Three feet from assembly, with left side closest; cataract in left eye 3 yr. after exposure; cataract in right eye 5 yr. after exposure
5	54	7	21	11	Six feet from assembly; lenses normal 3 yr. after exposure
6	21	5	15	9	Eight feet from assembly; lenses normal 3 yr. after exposure
7	23	2	6	4	Eight feet from assembly; lenses normal 3½ yr. after exposure
8	36	1.6	5	3	Sixteen feet from assembly; lenses normal 3 yr. after exposure
9	23	1.3	4	2	Sixteen feet from assembly; lenses normal 3½ yr. after exposure

examinations up to four years after exposure have failed to disclose any lenticular abnormalities. Victim 4, on the other hand, received about 45 rep to the left side of the head and an unknown, but certainly smaller, dose of fast neutrons to the right side. Epilation was pronounced on the left side of this patient's head. It is significant that examination of Victim 4 about 28 months after the accident failed to disclose any clinical manifestations of lens damage in either eye, but when he was reexamined, 32 months after the exposure, the left eye exhibited haziness in the posterior cortex, which developed within six months into a moderately advanced radiation cataract. It was not until 58 months after the exposure that the right eye began to display clinically observable opacities. It is reasonable to infer that the cataractogenic dose of fast neutrons for this victim was considerably less than 45 rep. The other survivors have experienced no lens abnormalities up to the present time (February, 1952), or, rather, no lens changes were on record at the time of their last examination. If some allowance is made for the age of Victim 5, who received an estimated dose of 21 rep, it seems probable that the cataractogenic dose of fast neutrons must lie somewhere above 15 rep, and considerably below 45 rep, for men in their 20's and early 30's.

CATARACT FROM EXPOSURE TO X-RAYS AND GAMMA RAYS

There is diversity of opinion as to what constitutes a cataractogenic dose of x-rays or gamma rays. Estimates run all the way from several hundred to several thousand roentgens. According to Hunt, the minimal dose for 100- to 200-kv. x-rays lies between 500 and 1,000 r. Merriam, on the other hand, concludes that a dose of at least 1,500 r is needed to produce cataract. These estimates are based on clinical data collected on patients who received radiation therapy to the head. There is great need for a further investigation of available clinical data along these lines. Up to the present, there is no evidence that x-ray or gamma-ray doses of a few hundred roentgens cause lens damage in man; indeed, it is probable that the cataractogenic dose is well above the $L.D._{50}$ in humans. However, recent exposures of mice and rabbits have shown that x-ray doses of between 100 and 250 r may cause lens damage in these species. Christenberry and his co-workers have been able to demonstrate lenticular abnormalities in mice with x-ray exposures as low as 32, and even 16, r. Cogan states categorically that the human lens is a relatively susceptible organ to x-radiation with the energies used in therapy (200 to 1,000 kv.) and that the threshold for production of cataract is less than that for any other gross abnormality of the eye or periocular tissue. Donaldson estimates 600 r as a tentative threshold dose for lens damage in man. In view of the low threshold doses found experimentally in other species and the wide variation in clinical data among humans, it seems wise to regard 500 r of x-rays or gamma rays as potentially dangerous to the human lens.

CONFERENCE ON RADIATION CATARACTS, FEBRUARY, 1950

In February, 1950, the Committee on Radiation Cataracts held a meeting in Washington to assess the present status of the problem and to plan a definitive research program. Funds were provided by the United States Atomic Energy Commission, with the request that they be administered by the National Research Council. At this time, there were 14 known cases of radiation cataract among physicists who had been associated with research employing the cyclotron.

A report by Evans in 1948 had shown that mice receiving small daily doses of fast neutrons and gamma rays from the cyclotron often exhibited cataracts. Comparable exposure to x-rays failed to produce cataract. His data on the chronic exposure of mice, whole body, to the radiations from the cyclotron, when compared with the effects of x-ray exposures, made it probable that fast neutrons were between 10 and 20 times as effective in producing cataract in mice as x-rays. These findings, and the unfortunate experiences of the cyclotron victims, aroused much interest in military and civilian circles. Scientists engaged in the development of nuclear weapons, nuclear power, civilian defense, and health physics were concerned, not to mention those engaged in nuclear research and in the medical and biological sciences.

Although a great deal of fundamental nuclear research had been going on among the physicists, it was apparent that little was known about radiation fluxes, energy spectra, and angular distribution of the neutrons and gamma rays emanating from cyclotron targets bombarded by protons and deuterons. For example, the fast-neutron flux emitted by a beryllium target bombarded by deuterons had not been appreciated generally. A current of 100 microamperes (μa) of 16-mev deuterons hitting a beryllium target produces about 20 rep a minute of fast neutrons having

energies above 3 mev, as determined with sulfur detectors. This dose rate is for the forward direction of the deuteron beam at a distance of 90 cm. from the target; at right angles to the beam the dose rate is approximately 5 rep a minute. A common laboratory procedure among physicists prior to 1949 consisted in shimming the magnetic field of the cyclotron while watching the glow from the target to determine the efficacy of the operation.

Radiation dosimetry for mixed beams of neutrons and gamma rays was not well developed at this time. Biologists and physicists, lacking suitable instrumentation, employed commercially available 25-r and 100-r Bakelite thimble chambers to determine fast-neutron doses in tissue. When the chamber is exposed to fast neutrons, the ionization reading of the 25-r chamber is called the (large) N unit of fast-neutron dose in tissue, while the reading of a 100-r chamber is called the (small) n unit. These units were estimated originally by Aebersold to correspond to about 2.5 rep of energy absorption in tissue by fast neutrons. Recent determinations by Rossi, Ham, and others indicate that the ionization reading should be multiplied by 2, rather than 2.5, to obtain the tissue dose in rep. It has been pointed out by Failla, Rossi, Ham, and others that such Bakelite thimble chambers do not give readings agreeing among themselves with any accuracy when exposed to the same beam of fast neutrons. Moreover, when these thimble chambers are exposed to a mixed beam of fast neutrons, thermal neutrons, and gamma rays, there is no reliable method of interpreting the results in terms of tissue dose. The radiations emitted by cyclotrons and nuclear reactors always consist of neutrons and gamma rays.

One objective of the Committee on Radiation Cataracts was to stimulate research on radiation dosimetry and to encourage comparisons among different laboratories so that the biological effects of ionizing radiations might be determined in terms of a common denominator. There have been several promising developments along the lines of mixed-radiation dosimetry. One method, developed at Oak Ridge by Hurst and his associates, utilizes a proportional counter surrounded by polyethylene (Polythene) and filled with a hydrogenous gas. The counter is designed on the Bragg-Gray principle; recoil protons engendered in the polyethylene radiator are counted as ionization pulses. An ingenious electronic method of pulse integration has been described by Glass and Hurst. One major advantage of this type of instrument is that it may be used to measure fast-neutron doses in the presence of a gamma radiation field. Since the ionization pulses from gamma rays are smaller than those arising from proton recoils, the former may be biased out without sacrificing any appreciable efficiency in the counting of proton recoils. Failla and Rossi have developed another approach to the dosimetry of mixed beams of radiation. Their instrument consists of an ionization chamber having walls of a tissue-like plastic and containing a gas which is also similar to tissue in composition. This ionization chamber will measure the number of ion pairs dissipated in tissue regardless of the nature or mixture of the radiations concerned. When placed in a mixed beam of neutrons and gamma rays, the tissue-wall, tissue-gas ionization chamber records the total number of ion pairs dissipated in tissue without differentiation as to the type of radiation depositing the energy. Within the past few months Hurst and Rossi have performed preliminary checks with the two types of instruments exposed to the same beam of mixed radiation. The results, to date, are most encouraging. It is possible by a process of subtraction to measure, accurately and separately, the fast-neutron and gamma-ray doses so that the relative biological effectiveness

of each component can be taken into account. Mixed-beam dosimetry is still a formidable problem for the health physicist, but these two instruments used in conjunction make it possible to measure the radiation components emanating from a cyclotron or a nuclear reactor. Rossi is attempting currently to develop a spherical chamber which has the combined features of a proportional counter and an ionization chamber.

Two primary objectives are to be kept in mind in planning a research program on radiation cataracts: first, the immediate and practical problem of attempting to ascertain the cataractogenic fast-neutron dose in humans to a higher degree of accuracy than was known from the scanty data on cataract victims; second, the need of promoting basic research on the biological effects of ionizing radiation as applied to the lens of the eye. The practical philosophy underlying the first objective was a determination of the cataractogenic fast-neutron dose in at least three species of animals, with the hope that if no large-scale variation among species were found, an extrapolation might be made to man. Also, if the relative biological effectiveness of x-rays or gamma rays and neutrons for the production of cataract should prove to be relatively constant for several widely differing species, it ought to be possible to derive the toleration dose of neutrons for man on the basis of a critical evaluation of the clinical records of patients who had received radiation therapy to the head with subsequent development of cataract.

A problem needing resolution was the capacity of tissue to recover after exposure to ionizing radiation. The practice of fractionation in radiation therapy is based on the demonstrated ability of tissue to recover partially from x-ray damage. Was this true for neutron irradiation? Were the effects of neutron irradiation completely irreversible, or only partially so? Questions of this nature indicated a need for data on animals subjected to both acute and chronic exposures of neutrons and x-rays or gamma rays. Many experiments in radiobiology had indicated a possible large-scale difference between x-rays and neutrons when delivered in small, fractionated doses. The fact that chronic doses of neutrons seemed highly additive was primary evidence of some difference in biological effect between x-rays and neutrons. Current thinking in radiobiology stresses the role of heavily ionizing particles, such as high-speed protons, in producing cell damage. Some of the effects of the spatial distribution of ion pairs in tissue (specific ion density) are discussed briefly by Ham in the appendix to the Proceedings of the First Conference on Radiation Cataracts. Was lens damage the result of direct hits on vulnerable material within the cell (the so-called target theory) or the result of indirect effects (chemical changes brought about by the production of H and OH radicals in aqueous media)? There is a growing tendency among radiobiologists to think of cell damage in terms of chemical changes induced by oxidative or reductive radicals engendered in solutions by ionizing radiation. Support for this thesis is to be found in experiments demonstrating the protective effect of certain chemicals and in the production by chemicals of cellular damage similar to that resulting from radiation exposure. Most of the experiments on aerobic versus anaerobic irradiation seem to be best interpreted in terms of some form of indirect mechanism involving chemical radicals. Gray has published recently an excellent review on the biological actions of ionizing radiations.

Another problem needing investigation was the possible effect of neutron energy on lens damage. Dose for dose, were 14-mev neutrons and 300-kev neutrons equally effective in producing cataract? The possibility of systemic effects in the production

of cataract (whole-body irradiation versus irradiation of the eye or head alone) could not be ruled out. Was radiation cataract a purely local effect, or were there contributing causes from the biological ensemble? Age was another variable which had to be considered in attempting to determine susceptibility to cataract. All available data indicate that the young and still actively growing lens is more sensitive to radiation damage than the mature lens and that both the latent period before onset and the severity of the lesion seem to be definite functions of age, as well as of magnitude of dose. A fascinating problem was whether the slow growth rate of the lens could be related to the long latent period between exposure to radiation and the development of cataract. Poppe's experiments in 1942 first suggested that some of the pecularities of radiation-induced cataract might arise from the fact that in the lens new fibers are continually being laid down throughout life by slow proliferation of the epithelial cells. Little was known in 1950 regarding the growth rate and mitotic index of lens epithelium. Some investigators were of the opinion that mitosis was too infrequent to allow an accurate determination of cell division.

In the remainder of this paper, an attempt will be made to discuss some of the experiments which have helped to clarify the problems facing the Committee on Radiation Cataracts in 1950. Many of these problems still await solution, but definite progress has been made in the interim.

EXPERIMENTAL STUDIES ON RADIATION CATARACT

Cyclotron Irradiation Versus X-Irradiation in Mice.—Evans has confirmed some of his earlier data on mice exposed to x-rays and to fast neutrons from the cyclotron. For acute exposures, using the $L.D._{50}$ as the biological criterion, he finds that neutrons from the cyclotron are 2.5 times as effective as x-rays in producing death. Complete opacification of the lens in 50% of the mice within one year was produced by 80 rep of fast neutrons delivered as an acute dose. The same dose produced visible opacities in all his mice within one year. Determination of comparable effects on the lens by means of whole-body x-irradiation was not feasible because most of the mice died before the onset of cataract; this problem was solved by shielding the bodies of the mice and delivering x-rays to the head alone. Thus, Evans compares whole-body neutron irradiation from the cyclotron with x-irradiation to the head alone. Preliminary data on acute exposures under these conditions result in a relative biological effectiveness of about 9 for the production of visible opacities; that is, 700 r to the head alone corresponds to 80 rep of neutrons in producing visible opacities in 100% of the mice. Evans is experimenting currently with chronic exposures in an attempt to define more accurately the relative biological effectiveness for cataract. There is little doubt that biological effectiveness ratios in excess of 10 will be obtained, since, on the basis of past experience, some recovery between x-ray exposures is to be expected, whereas repeated small doses of neutrons are highly additive.

Cyclotron exposures employing a beam of deuterons on an internal beryllium target produce large quantities of hard gamma rays, as well as neutrons with energies extending from 15 mev down to epithermal and thermal energies. The energy spectrum of the fast neutrons has a broad peak at about 5 or 6 mev. Abelson has shown by means of sulfur detectors that roughly 50% of the total tissue dose in the forward direction of the deuteron beam is composed of fast neutrons with energies above 3 mev. As a first approximation, it is usual to assume that fast neutrons contribute the major portion of the tissue dose; lead shielding can be used to reduce

the gamma-ray exposure without affecting appreciably the fast-neutron beam. The efficiency of deuterons on beryllium in producing fast neutrons makes the cyclotron an excellent accelerator for acute exposures. About 1 fast neutron is produced for every 1,000 deuterons striking the target, and it is not uncommon in modern laboratory practice to obtain deuteron beams of several hundred microamperes. However, the mixed nature of the radiation beam introduces dosimetry problems which complicate the experiment of the radiobiologist. More elegant from the standpoint of pure neutron beams and exact dosimetry are some of the available reactions with the Van de Graaff and Cockcroft-Walton accelerators. The efficiencies of the D-D (deuterons bombarding deuterium) and the D-T (deuterons bombarding tritium) reactions are sufficient for biological exposures. These reactions can be used to provide a monoenergetic neutron beam of almost any desired energy and have the advantage of being uncontaminated with gamma rays and slow neutrons. Rather lengthy exposure times are required for acute radiation studies, but the method is ideal for chronic exposure studies. As an example of this type, the Cockcroft-Walton accelerator at Los Alamos requires about one and a half hours to deliver a dose of 250 rep of 14 mev neutrons at an irradiation distance of 10 cm. from the target, with use of the D-T reaction.

Slater has described radiation-exposure techniques developed at Oak Ridge for chronic studies. Plaques employing a number of polonium-beryllium sources of fast neutrons have been designed to provide a radiation field of fast neutrons which is constant within 15 to 20% over a large volume. Large animals or many small animals may be irradiated at a suitable dose rate for chronic experiments. The gamma-ray background of these neutron sources is negligible, and the radiation dosimetry can be performed with accuracy. The energy spectrum of the fast neutrons is reasonably well known. The neutron sources can be augmented or replaced with Co^{60} gamma-ray sources for mixed radiation-beam investigations or for pure gamma-ray exposure studies. Byrnes and associates are using these techniques to expose animals to fast neutrons and to gamma rays. The "swimming-pool" nuclear reactor at Oak Ridge can be used also to expose animals to chronic doses of mixed beams composed of neutrons and gamma rays. However, the dosimetry problems encountered with the reactor are somewhat formidable.

Allen and his co-workers, at the University of Pittsburgh, have succeeded in bringing a beam of 15-mev deuterons out of their cyclotron and allowing it to impinge on an outside target, which is well shielded and far removed from the cyclotron proper. This procedure provides an excellent source of fast neutrons with a much smaller percentage of gamma rays in the beam than can be obtained with a target situated within the cyclotron. The head of an experimental animal can be placed close to the outside target in a manner to take full advantage of the law of the inverse square to minimize whole-body irradiation. Acute exposures of several hundred reps of fast neutrons can be delivered to the head without sacrificing the animal to lethal doses of whole-body radiation. Moses and Linn have used this arrangement to study the production of radiation cataract in dogs. Their data indicate that dogs may be less susceptible to lens damage than other mammalian species, but they recommend caution in accepting this apparent variation among species until a more careful analysis of the problem of radiation dosimetry has been made.

Exposures of Mice to X-Rays and Slow Neutrons from the Thermal Column.—Furth, Christenberry, Upton, and Sheppard have exposed mice to x-rays and to thermal neutrons produced in the nuclear reactor at Oak Ridge. Before their findings are discussed, it is necessary to describe their method of grading lens damage in mice. By using the slit lamp, they are able to detect changes in the lens which are not ordinarily observable with the ophthalmoscope. Ophthalmologists are in general agreement that it is difficult, if not impossible, to define a true threshold value for radiation cataract; the tendency is to regard lenticular abnormalities which do not affect visual acuity, or at least are not observable with the ophthalmoscope, as representing negligible damage from a practical standpoint. However, sensitive criteria of lens damage are desirable, especially as an early indication of radiation injury to the lens. The Oak Ridge group recognizes four grades of lens damage in mice. Apparently, a Grade I lesion is observable only with the slit lamp, whereas a Grade II lesion can often be seen with the ophthalmoscope but does not necessarily constitute a visible opacity which would interfere with vision; a Grade III lesion seems to be equivalent to a visible opacity which would interfere with vision, and a Grade IV lesion constitutes a mature radiation cataract with partial, if not complete, opacification.

At Oak Ridge, the $L.D._{50}$ of mice exposed to slow neutrons from the thermal column of the nuclear reactor was compared with that of mice receiving whole-body x-ray exposures. Eighty minutes' exposure to a thermal neutron flux of 9×10^8 $n/cm.^2/sec.$/plus an estimated 4 to 8 r of hard gamma rays was found to be equivalent to an 80-minute exposure to 250-kvp x-rays at a dose rate of 6.4 r a minute. A rough calculation indicates that about 300 rep of slow neutrons produced the same lethal effect as 512 r of x-rays, a relative biological effectiveness of approximately 1.5 for lethality. During these experiments, cataracts made their appearance 70 to 80 days after exposure; the incidence of lens damage at all dose levels was greater for the mice exposed to the thermal column than for those exposed to a comparable dose of x-rays. Sufficient data are not available to allow any quantitative estimates of the relative biological effectiveness for x-rays versus thermal neutrons in the production of cataract, and about all that can be judged is that thermal neutrons are more effective than x-rays in producing lens damage. Grade-I abnormalities of the lens were observed in mice exposed to 30, and even to 16, r of x-radiation over the whole body. Grade-III and Grade-IV damage to the lens was seen only in animals receiving 120 r or more of x-rays.

Brennan and associates have made an exhaustive study of the experimental conditions accompanying the exposure of mice within the thermal column attached to the homogeneous reactor (water boiler) at Los Alamos. Female Swiss mice were exposed to x-rays from a 250-kvp machine and to the mixed radiation in the thermal column. Correction factors were applied for (1) inherent gamma-ray contamination in the column, (2) the intermouse gamma-ray dose due to hydrogen-capture gamma rays, and (3) attenuation of the thermal neutron flux in the exposure cavity by the "sink" effect of the mass of mice. The relative biological effectiveness of x-rays versus thermal neutrons was found to be 1.7, the $L.D._{50}$ (death in 30 days) being used as the biological criterion and acute exposures being employed.

Storer and associates have exposed white female Swiss mice under the general experimental conditions outlined in the Brennan report wth the objective of studying the incidence of lens opacities and of determining a relative biological effectiveness

for exposure to 250-kvp x-rays and to thermal neutrons from the thermal column of the homogeneous reactor. They define as "lens opacities" all abnormalities of the lens characteristic of radiation damage and visible with the ophthalmoscope; the first examination at which an opacity which subsequently persisted was seen is taken as the end-point of the latent period for its production. The mice were observed for 30 weeks, and the incidence and latent period of radiation-induced lens opacities were determined as a function of the radiation dose. X-ray doses of 200 r or more produced opacities in 100% of the animals. It was found that the higher the dose the shorter the latent period before the appearance of opacities; this was true for both types of radiation exposure. The data showed that 4.7 seconds of thermal-column exposure was equivalent to 44.4 seconds of x-ray exposure in producing the lens opacities in 50% of the animals 30 weeks after exposure. Taking the rep as 93 ergs per gram of tissue and expressing all radiation doses in terms of reps, it appears that 2.9 rep of thermal neutrons plus 1.7 rep of inherent gamma rays (approximate energy 4 mev) plus 0.5 rep of intermouse gamma rays (energy 2.2 mev) was equivalent to 39.4 rep of 250-kvp x-rays. Any calculation of relative biological effectiveness necessarily involves a knowledge of the biological effectiveness ratio of 4-mev gamma rays and 2.2-mev gamma rays versus 250-kvp x-rays for the production of lens opacities. On the assumption that biological effectiveness ratios for these gamma rays are the same as for the $L.D._{50}$ studies determined by Brennan, Storer concludes tentatively that thermal neutrons are roughly 15 times as effective as 250-kvp x-rays in producing lens opacities. Even if these hard gamma rays are assigned a relative biological effectiveness of 1 in comparison with x-rays, the relative biological effectiveness of x-rays versus thermal neutrons for lens opacities emerges as the order of magnitude of 13 or 14. It is difficult to understand how thermal neutrons can be more effective than fast neutrons in the production of lens opacities. Most of the energy dissipated in tissue by fast neutrons goes into the production of proton recoils, whereas only those thermal neutrons captured by nitrogen, or possibly by traces of boron, produce heavily ionizing particles in tissue. It is admittedly difficult to calculate the energy dissipated in a small mouse by thermal neutrons, partly because of the uncertainty as to what proportion of the hard gamma rays (2.2 mev) engendered by hydrogen capture of thermal neutrons is deposited in the body of the mouse. Harris estimates that only 2 or 3% of the total dose comes from hydrogen-capture gamma rays. Inaccuracies in the calculation of the tissue dose deposited by thermal neutrons can alter the relative biological effectiveness materially. Storer and Harris have recalculated their data, taking into account the peaking effect of thermal neutron dose 3 mm. within tissue, as shown by Snyder. They conclude that the relative biological effectiveness of x-rays versus thermal neutrons should be revised downward from 15 to about 6. Mice display a congenital tendency toward lens opacities, as shown by the fact that opacities often develop in controls which have received no radiation exposure. It is possible that species variation of this type might help to explain these high biological effectiveness ratios for x-rays versus thermal neutrons. It should be pointed out that no definitive studies comparable to those of Storer have been made on the production of lens opacities by fast neutrons in mice. It is probable that relative biological effectiveness for initial lens damage in mice as a result of fast-neutron exposures is in considerable excess of that found for thermal neutrons.

Exposures of Mice at Operation Greenhouse.—LeRoy and the group at Oak Ridge (Furth, Christenberry, Upton, and Sheppard) collaborated in a study concerned with the incidence of lens damage among mice exposed to atomic bomb radiations at Operation Greenhouse. In order that relatively pure gamma-ray exposures might be insured, mice enclosed in bomb-proof aluminum containers were placed at various distances from the explosion, where the fast-neutron exposure would be relatively unimportant in comparison with the gamma-ray dose. Forty-five hundred mice were exposed to gamma-ray doses ranging from 1,300 to 180 r. The $L.D._{50}$ for gamma rays from the bomb was found to be 750 r. At the distance from the bomb where 750 r was received, the fast-neutron exposure was estimated to be less than 1 rep. While this estimate may be low, it is probable that the fast-neutron dose was under 10 rep. Mice surviving the $L.D._{50}$ exposure of gamma rays exhibited lens damage by the end of the third month; mature radiation cataracts developed eventually in all these mice. Mice exposed to the lowest gamma-ray dose, 180 r, had observable changes in the lens (Grade I and Grade II lesions).

Relatively pure neutron exposures were obtained by placing mice in special bomb-proof containers shielded by 7 in. (17.8 cm.) of lead. Fast- and thermal-neutron doses within the containers were estimated from sulfur and gold detectors. Six hundred forty mice were placed at various stations, where the fast-neutron doses varied from about 600 down to about 1 rep. Even at the farthest station, where the mice were estimated to have received between 1 and 10 rep of fast neutrons and about 1 r of gamma rays, Grade I and Grade II, changes developed in the lens. The unavoidable dosimetry problems encountered on these bomb exposures make it difficult to assess the results, but the experiments are in general accord with those of other investigations and support the conclusion that neutrons are much more effective in producing lenticular damage than gamma rays.

Exposures of Rabbits and Monkeys to X-Rays, Gamma Rays, and Fast Neutrons.—Cogan and Donaldson have studied lens damage in chinchilla rabbits after acute exposures to 1,200-kv. (constant potential) x-rays. Radiation cataracts appeared with a latent period that was an inverse function of the dose. The threshold dose was estimated to be 250 r or less for 10-week-old rabbits, and the younger the animal the shorter the latent period for the development of radiation cataracts. The body of the rabbits was shielded; for doses of less than 1,000 r cataract was the only biological abnormality produced.

As a complement to the hard x-ray exposures of rabbits, Cogan, Goff, and Graves exposed 10-week-old, French silver rabbits to pure neutron beams of 14 mev, produced by bombarding tritium with deuterons from the Cockcroft-Walton accelerator at Los Alamos. Duplicate exposures to 300-kev neutrons were performed on the so-called fast reactor. The purpose here was to determine any differences in the cataractogenic properties of fast neutrons having widely different energies. Gamma rays were completely negligible in both these types of exposures. The animals were positioned in a manner to take full advantage of the law of the inverse square in order to reduce whole-body exposure to a minimum, and no animals died as a result of whole-body exposures. Four or five rabbits were exposed simultaneously to acute doses, which took an exposure time of from one to six hours, depending on the total dose delivered. The course of events following neutron irradiation was basically similar to that following x-ray exposures. The degree of lens damage after exposure

to 8×10^9 n/cm.^{2} of 14-mev neutrons corresponded to that after 30×10^9 n/cm.^{2} of 300-kev neutrons; this damage was comparable to that produced by 500 r of 1,200-kv. x-rays.

Calculations of neutron tissue dose based on Mitchell's work and the more elaborate investigations by Snyder make it possible to estimate the tissue dose in reps from Cogan's and Donaldson's data. Thus, 8×10^9 n/cm.^{2} of 14-mev neutrons corresponds to about 40 rep, while 30×10^9 n/cm.^{2} of 300-kev neutrons corresponds to about 50 rep. The dependence on neutron energy does not appear to be critical in the production of lens damage, being a factor of about 1.25 between 14-mev and 300-kev neutrons. When the dose of 40 rep of 14-mev neutrons is compared with 500 r of 1,200-kv x-rays for comparable lens damage, a relative biological effectiveness of about 11 results; similarly, for 300-kev neutrons, the relative biological effectiveness is about 9. These biological effectiveness ratios compare favorably with Evans' data on mice exposed to the neutron beam from the cyclotron and to 250-kvp x-rays. They are higher than the revised relative biological effectiveness for x-rays versus thermal neutrons given by Storer and Harris. An experiment similar to Cogan's in which he used the Cockcroft-Walton accelerator at Los Alamos should be made on mice, so that the relative effectiveness of thermal versus fast neutrons could be determined on the same species. Cogan estimates that the threshold dose for production of lens damage which is detectable with the ophthalmoscope in rabbits is less than 2×10^9 n/cm.^{2}, or about 10 rep for 14-mev neutrons. The corresponding threshold for 1,200-kv. x-rays is about 250 r. Thus, the relative biological effectiveness for detectable threshold damage is roughly 22 in rabbits, a value which is considerably higher than Storer's relative biological effectiveness for thermal neutrons. This is in accord with modern radiobiological thinking regarding the role of heavily ionizing particles in tissue damage. It seems quite likely that both Cogan's and Storer's biological effectiveness ratios in rabbits and mice are much larger for threshold evaluations of lens damage, whereas if more extensive damage is used as the biological criterion, the biological effectiveness ratio of neutrons and x-rays becomes correspondingly smaller.

Goff has made follow-up studies over a long period on rabbits exposed to the Cockcroft-Walton accelerator. In some instances he has noted considerable regression in lens opacities. He is also in the process of evaluating recent chronic exposures of rabbits to 14-mev neutrons from the D-T reaction. The completion of this experiment will provide valuable data on the much discussed reversibility with time of fast-neutron tissue damage, since the effects of chronic and acute exposures to the same beam of fast neutrons can be compared on the same species. The problem of chronic exposures of human personnel to ionizing radiation is a very real one and deserves more study in experimental animals. It is desirable that the Los Alamos group be encouraged to expose mice also to fractionated doses of 14-mev neutrons on the Cockcroft-Walton accelerator. This would provide additional data on the reversibility with time of fast-neutron damage to tissue.

Boag has described recent radiation cataract research in England. Tansley, Howard, and Gray are exposing rabbits to fast neutrons produced with a Van de Graaff accelerator. In addition to ophthalmological examinations, cytological research on the lens epithelium of rabbits is in progress. Howard has evolved a special technique for preparing flat slides of rabbit lens epithelium; this technique makes it possible to study cell division and to detect cellular damage by the employment of suitable staining procedures.

Byrnes and associates have outlined an extensive program on simians which is being supported by the Air Force. Monkeys have been exposed recently (January, 1953) to acute doses of 14-mev neutrons and to mixed beams of fast neutrons and gamma rays in fractionated doses. Future plans call for acute exposures to slow neutrons in the thermal column and for chronic exposures to relatively pure beams of fast neutrons and gamma rays. The completion of this simian program will contribute a wealth of data on another species than rabbits and mice.

GROSS ANATOMY OF THE EYE

Before discussion of some of the more recent experiments on biological mechanisms leading to radiation cataract in the mammalian lens, it will be helpful to describe some of the gross features of lens anatomy. The cornea in man is about 0.6 to 0.8 mm. thick. Behind the cornea is the anterior chamber, filled with aqueous humor. The maximum depth of the anterior chamber is along its central axis, being about 3 to 3.6 mm., so that the maximum distance from the anterior surface of the cornea to the anterior surface of the lens is about 4 mm. The iris separates the anterior chamber from the posterior chamber, which is also filled with aqueous humor. The vitreous body, a clear, transparent gel of semisolid consistency, fills the chamber of the eyeball behind the lens. The lens has no direct blood supply and must rely on the nutrient fluid bathing its surface for metabolism. The aqueous may be regarded as a dialysate of the blood serum, containing oxygen in solution and metabolites needed by the lens.

The lens is a transparent structure having a biconvex shape with a rounded border, the equator. The anterior surface is curved as a flattened ellipsoid, the curvature culminating in a central anterior pole. The posterior surface is more highly curved, as a paraboloid, culminating in a central posterior pole. The central axis, from pole to pole, is about 4 mm. in diameter, while the equatorial diameter is about 9 mm. The average weight of a mature human lens is about 0.2 gm. and the average volume about 0.2 ml.; the water content is about 65% by weight, and the protein, and hence the nitrogen, content of the lens is high compared with that of other tissues, being a little more than 4% nitrogen by weight. Structurally, the lens is divided into three parts: the capsule, the epithelium, and the lens substance. The capsule is a tough, clear membrane entirely surrounding the rest of the lens; it has a thickness of about 12 to 14 μ at the anterior pole. The epithelium extends as a single layer of highly viable cells under the anterior capsule as far as the equator. There are no epithelial cells on the posterior subcapsular surface of the lens beyond the equator. Toward the equator, in the anterior peripheral zone, the epithelial cells become smaller and more cylindrical. This is the germinative zone, where mitotic activity is pronounced as compared with that in the relatively static anterior central area. Near the equator, the epithelial cells tend to become arranged in meridional rows, and their inner parts become elongated and orient themselves obliquely to run up beneath the epithelium of the anterior capsule. At this stage the epithelial cells are more correctly characterized as young lens fibers.

There is a constant laying down of new lens fibers at the equator; the deeper one goes into the lens substance, the older are the fibers encountered, so that at the center of the nucleus are found those oldest fibers which were laid down in fetal life. The interior of the lens is stratified into zones, which can be distinguished with the aid of the slit lamp. There are an embryonic and fetal nucleus, composed of the

oldest fibers; an adult nuclear zone, composed of fibers formed during early life, and the cortex, composed of those younger and more superficial fibers which lie between the nucleus and the capsule. The lens is rather unique among mammalian organs in that it grows very slowly, but continuously, throughout life, without being able to slough off old cells because of the lens capsule. This is not to say that the lens is not in a dynamic state with regard to metabolites, according to the concept first clearly enunciated by Schoenheimer; on the contrary, some of the metabolic turnover rates have been explored by means of radioactive tracers. However, other generative tissues, such as skin and bone marrow, are continually shedding old cells, whereas the epithelial cells behind the capsule of the lens differentiate into lens fibers which remain within the nucleus or cortex throughout life. There is no mechanism whereby the lens can rid itself, on a cytological scale, of abnormal, damaged, or nonviable cells. This may be a primary reason for susceptibility of the lens to radiation damage, as pointed out by Poppe in 1942.

EFFECT OF RADIATION ON LENS EPITHELIUM IN RABBITS

Von Sallmann has conducted some interesting investigations on the effect of x-rays on the mitotic activity and nuclear fragmentation of the lens epithelium in normal and in cysteine-treated rabbits. He has applied a technique perfected by Howard for the preparation of total flat mounts of lens epithelium attached to the capsule. This method provided a means of obtaining reliable estimates of the mitotic index in normal rabbits and suggested the possibility of studying the influence of ionizing radiation on cell division, as well as the possible protection afforded by chemical substances such as cysteine. The Feulgen-positive staining technique was used for counting cells in mitosis and for detecting signs of early nuclear damage in cells which had been irradiated. Chinchilla rabbits, 12 to 16 weeks old, were used for an analysis of cell division; von Sallmann employed 100 rabbits and examined 200 preparations of lens epithelium.

The number of cell elements was estimated to be approximately 790,000 in the normal, mature rabbits on the basis of cell counts for preparations of the entire epithelium. The mitotic index for the total preparation of epithelium ranged from 18 : 100,000 to 27 : 100,000 in the rabbits examined. The distribution of dividing cells varied characteristically in the several anatomic zones of the epithelium. The highest index (60 : 100,000) was found in the germinative zone; this contrasted with an index of 0.11 : 100,000 in the spacious central area, and with the apparent absence of dividing cells in the nuclei of the lens bow.

Exposure to 1,500 r of x-rays was followed by almost complete disappearance of dividing cells within 30 minutes. Total inhibition lasted from three to four days, to be followed by recovery of mitotic activity within the next four days. This, in turn, was followed by a period of overcompensating increase in the proportion of dividing cells, which persisted for at least another week. Nuclear fragmentation and extrusion of Feulgen-positive material were observed after irradiation. Since those cells which have entered mitosis at the time of exposure to x-rays presumably complete the cycle, the cessation of mitosis 30 minutes after irradiation indicated that the time required for mitosis was about 30 minutes. There was a steep rise in the incidence of nuclear damage when the inhibition of mitosis terminated, particularly when the overshooting phenomenon had developed fully. Among the pathologic reactions observed were clumped chromosomes, translocation of chromosomal mate-

rial with a tendency to form bridges, and nuclear fragmentation. A drastic depletion of cellular elements in the germinative zone was observed three months after irradiation. This observation confirmed the common radiobiological experience that nuclear destruction is encountered predominantly in regions of active cellular proliferation and may be considered a precursor of subsequent depletion of viable cells.

The injection of cysteine prior to irradiation prolonged the inhibitory effect of x-rays in mitosis, slowed the speed of recovery, and reduced the extent of overshooting in cell division. The protective action of pretreatment with cysteine was demonstrated by a lower incidence of nuclear fragmentation in all zones, as compared with the incidence of this type of damage in the eyes of untreated rabbits which had been irradiated and of rabbits given injections of cysteine after irradiation.

Von Sallmann's painstaking research demonstrates clearly that cytological damage from ionizing radiation can be detected in the lens epithelium prior to clinical manifestations of lens damage. Similar findings by Poppe in 1942 and Cogan in 1951 are amply confirmed and emphasize the growing conviction among ophthalmologists that the primary site of radiation damage, leading eventually to radiation cataract, is in the lens epithelium. Von Sallmann is the first to obtain convincing mitotic indices for the different regions of the epithelium and to show the influence of ionizing radiation on the mitotic index. His research indicates that the maximum damage from x-rays occurs where the cells are proliferating most actively, namely, in the germinative zone; and his demonstration of the protective action of cysteine stimulates hope that eventually some type of chemical protection against ionizing radiation may be perfected to the stage where personnel undergoing radiation exposure in line of duty may be given preexposure treatment with palliative results. It is to be hoped that techniques similar to von Sallmann's can be used to uncover possible differences in the biological actions of x-rays and neutrons.

Recently, von Sallmann, Tobias, and Munoz have given a preliminary report on the effects of deuterons and alpha particles on the rabbit lens. Deuterons and alpha particles with sufficient energy to penetrate into the lens were obtained on an accelerator at the University of California. Special techniques were used to irradiate either the anterior central surface or the equatorial region of the lens. Preliminary data indicate that maximum damage results from irradiating the equatorial region, and much smaller doses are needed here than at the central anterior region to produce comparable damage to the lens. The data also support the prevalent belief that heavily ionizing particles are more effective than x-rays in producing damage to the lens. A complete report on this research will be awaited with interest, since this is the first time that it has been possible to irradiate the lens proper with primary deuterons, protons, and alpha particles. Cytological data on the specific role of ion density in producing cellular damage in the epithelium of the lens are needed badly.

Cogan and Donaldson also have contributed convincing evidence of cytological damage to the lens epithelium of rabbits exposed to 1,200-kv. x-rays. After exposures of 1,500 to 2,000 r, they have observed such phenomena as cells with abnormally large amounts of cytoplasm and cells with multiple nuclei and striking karyorrhexis. Flat preparations of the posterior capsules of rabbit lenses 100 days after exposure to a dose of 2,000 r were found to have aberrant cells affixed to the capsule. In the early stages of cataract formation at the posterior pole, and before the subjacent cortex undergoes changes leading to opacification, these abortive cells may be rubbed off prior to fixation with a spatula, leaving a clear capsule beneath.

PATHOGENESIS OF RADIATION CATARACT

A puzzling problem is how manifestations of radiation cataract first appear clinically at the posterior pole of the lens when the truly viable cells are located entirely on the anterior surface of the lens beneath the capsule. Cogan has presented some fruitful observations regarding the pathogenesis of radiation cataract based on his observations in 20 cases among bomb victims, cyclotron physicists, and other persons receiving radiation therapy to the head. He was able to collect 26 human lenses which had been removed from cataractous patients. The cytological changes in the epithelium, preceding the opacification of the lens, suggest a disturbance of cell differentiation and were compatible with the hypothesis that radiation disrupts normal cell division. Some epithelial cells are killed by the radiation dose; others undergo metamorphosis—aberrant mitosis—whereby they become monster cells, with abnormal cytoplasmic content and multiple nuclei. Whether these monster cells die or develop further does not seem to be known. Other cells are damaged by the radiation and show their abnormality when they start to differentiate into lens fibers near the equator. These cells survive, and perhaps divide, but they can no longer fulfill their destiny of becoming young lens fibers at the equator; rather, they remain globular or ellipsoidal and form, at best, abortive processes. Then, apparently, they migrate, or are pushed, toward the posterior pole between the cortex and the capsule, where they form the characteristic opacity of early radiation cataract. Whether this migration is active or passive is not clear, but they move beneath the only potential space available and come to lodge finally in the central area around the posterior pole of the lens. This seems to be the place of least mechanical resistance to the piling up of damaged cells. What relation these cells have to the later opacification of the subjacent cortex is conjectural; it seems reasonable to assume that it is the degeneration of these damaged cells, with liberation of their intracellular enzymes, that causes the lysis of the cortex. The most characteristic observation in early radiation cataract is the migration of these aberrant cells while the lens appears otherwise perfectly normal.

There is disagreement among ophthalmologists as to whether early manifestations of radiation cataract can be seen first at the equator or at the posterior pole of the lens. In man, the equator is not readily visible on clinical examination, and this may explain why opacities are observed first at the posterior pole. In rabbits, on the other hand, lens damage is seen often at the equator before it can be observed at the posterior pole, according to Leinfelder.

PERMEABILITY STUDIES ON NORMAL AND CATARACTOUS LENSES

Radioactive tracer techniques have been employed by von Sallmann to study the permeability of normal and cataractous lenses. Radioactive indicators (Na^{24}, K^{42}, I^{131}, and P^{32}) served as tools. Specific activities in the serum, in the aqueous, and in normal and x-irradiated lenses were measured by standard counting techniques or by densitometry on radioautographs. There was no difference in the uptake of radioactive sodium by normal and by irradiated lenses immediately after exposure, but the uptake was greater in irradiated lenses after cataract had set in, and this uptake increased with the progress of opacification. Radioactive potassium penetrated well in the normal lens; there appeared to be a slight decrease in the exchange of radioactive potassium with the potassium of the cataractous lens. The accumula-

tion of radioactive iodine in irradiated lenses showing initial cataractous changes exceeded the accumulation in normal lenses. This was not true for irradiated lenses prior to the onset of cataractous changes. Radioactive phosphorus accumulated in normal lenses principally at the equator and in the surface layers of the cortex. The differences between the cortical and the deeper portions vanished in lenses with total radiation cataract, but the autographs of normal lenses and of lenses with initial radiation damage were the same. These investigations do not lend support to the theory that changes in the permeability of the lens are caused by ionizing radiation and that this results in initial changes leading to radiation cataract. They suggest, rather, that changes in permeability accompany, and perhaps influence, the progress of opacification.

BIOCHEMISTRY OF THE MAMMALIAN LENS

Kinsey and Merriam have contributed valuable data on the biochemistry of the mammalian lens. Their studies demonstrate that the Schoenheimer concept of the dynamic state of body constituents applies equally well to the avascular lens as to other tissues having a direct blood supply. A modified Warburg technique was developed to culture the lens in vitro. The synthesis of glutathione, which is concentrated highly in the mammalian lens, was studied. Radioactive glycine (aminoacetic acid) was added to the culture medium, and rabbit lenses were cultured for 24 hours. The tagged glycine was taken up in the various portions of the lens, and some of it was incorporated into glutathione, which is a tripeptide containing glycine as one of its constituent amino acids. Half of the glutathione content of the lens was turned over within 24 to 28 hours. The average rate of turnover of glycine in lens glutathione was 2.35% per hour, and the turnover rate of glycine in protein was of the same order of magnitude. These observations suggest that glutathione and proteins in the lens are being continuously synthesized from their constituent amino acids. The rates of turnover of glutathione in lenses removed from animals which had been fed naphthalene were greatly reduced. Naphthalene is known to produce cataract when fed to experimental animals. The reduced concentration of glutathione known to be associated with the cataractogenic process is thought to result primarily from an inhibition of glutathione synthesis, probably through poisoning of either the enzyme systems directly responsible for synthesis or those responsible for providing energy for the synthetic processes.

The more recent studies of Kinsey and Frohman on the enzyme systems operating in the lens give biochemical support to the belief that the lens epithelium may be the initial site of radiation injury. They investigated the sources of energy available to the lens for synthesis. Cytochrome c was isolated in relatively pure form from the epithelium of 40 bovine lenses. Previous attempts by other investigators to demonstrate the presence of the cytochrome system in appreciable amounts within the mammalian lens had met with little success because whole lenses had been used for the analysis. Kinsey and Frohman separated the epithelium and capsule from the rest of the lens before performing their analysis and found almost 200 mg. of cytochrome c per 100 gm. of epithelial tissue. They also found that riboflavin was present in the epithelium in concentrations 100 times as great as in the cortex. These findings demonstrate the existence of a respiratory enzyme system which is confined almost entirely to the epithelium of the lens.

The cytochrome and riboflavin systems in the epithelium appear to function in the oxidation of carbohydrate, and not solely in the oxidation of amino acids or fats. This deduction comes from a consideration of the concentration of lactate and pyruvate in the epithelium, cortex, and nucleus of the rabbit lens. The data indicate that the epithelium contains an unusually high concentration of pyruvate and a low concentration of lactate, whereas the cortex and nucleus contain a high concentration of lactate and a negligible concentration of pyruvate. Two hydrogen atoms are released in the over-all process involving the oxidation of glucose to pyruvic acid. In the absence of a cytochrome system, it is difficult to understand how these hydrogen atoms can combine with oxygen to form water; accordingly, they must combine with pyruvate to form lactate if metabolism is to continue. In tissue lacking the cytochrome system, as seems to be the case for the cortex and nucleus of the lens, the amount of lactate formed would be greater than in tissue where this enzyme system is functioning to oxidize carbohydrate. The deficiency of lactate in the epithelium is taken to mean, therefore, that the respiratory enzyme system functions, at least in part, in the breakdown of carbohydrate.

The lens epithelium appears to have a strictly aerobic type of metabolism, and the cortex and nucleus seem to have a strictly anaerobic type. The rate of oxygen consumption by the epithelium is extremely high in comparison with that of most other tissues. Since by far the greater amount of energy derived from the breakdown of carbohydrate is obtained aerobically, the fundamental differences in metabolism in the various parts of the lens suggest that an important function of the epithelium may be to furnish energy for the maintenance of the entire lens. Presumably, the only oxygen available to the lens is that which is dissolved in the aqueous. Nature seems to have provided a highly efficient process for the utilization of this limited supply of oxygen and has located the factory close to the source of supply.

Tissue usually derives its energy from energy-rich phosphate bonds. When adenosinetriphosphate is broken down to adenosine diphosphate, the energy available in the phosphate bond can be used in the presence of suitable enzymes for protein synthesis. The lens consumes about 3 mg. of glucose daily, and if only the anaerobic glycolytic process were utilizable, there would not be enough energy available to account for synthesis in the lens. Kinsey has shown that the supply of adenosinetriphosphate is highly concentrated in the epithelium but falls off rapidly in the interior of the lens. Von Sallmann also found that radioactive phosphorus accumulated principally at the equator and in the surface layers of the cortex. Adenosinetriphosphate is not available in sufficient quantities within the interior of the lens to supply its energy requirements, but phosphocreatine, which acts as a storage house for high-energy phosphate, has a concentration gradient in the opposite direction, being more abundant in the cortex than in the epithelium. Just how the epithelium can transfer energy to the cortex and nucleus for protein metabolism has not been determined, but Kinsey postulates some type of diffusion mechanism. He is continuing his studies on irradiated lenses cultured in vitro, directing special efforts toward an elucidation of the fate of adenosinetriphosphates and carbohydrates.

It is tempting to postulate that the inactivation by ionizing radiation of the enzyme systems functioning in the epithelium might account for von Sallmann's observations concerning the inhibition of mitosis. Cellular division requires the

production of large amounts of deoxyribonucleic acid, for example. Perhaps cellular division ceases temporarily because the epithelium can no longer supply the energy needed for synthesis. In vitro experiments indicate that it requires large doses of ionizing radiation to inactivate enzymes in aqueous solution, but it has been shown in at least one case that when the enzyme is spread out as a thin layer on the substrate, surprisingly small doses of radiation can cause inactivation. X-rays are more efficient than heavily ionizing particles, such as proton recoils or alpha particles, in inactivating enzymes in solution. Undoubtedly, several types of biological damage are occurring simultaneously when cells undergo irradiation, but it would be interesting to know whether neutrons are as effective as x-rays in causing the inhibition of mitosis noted by von Sallmann. Enzyme inactivation by ionizing radiation is a reversible process, or at least a process capable of repair with time, whereas nuclear damage, like fragmentation or extrusion of Feulgen-positive material, is regarded generally as a completely irreversible process. A comparison of the inhibition of mitotic activity and nuclear damage to the cell structure as a function of comparable doses of x-rays and neutrons might uncover interesting phenomena regarding the role of these radiations in producing biological injury and might help to explain why the damage caused by neutrons is seemingly more irreversible than that caused by x-rays. It is probable that high specific ion densities are more effective in producing nuclear damage of the irreversible type than low-density ion tracks, it being postulated by some radiobiologists that more than one ion pair is needed within a given area to produce the effect. In the case of enzymes, however, it is believed that one ion pair is generally sufficient to inactivate the molecule. Certainly, the production of H and OH radicals in aqueous media must be operative in producing chemical changes in the capsule and epithelium, as well as in the aqueous humor. The possibilities for further research on lens injury by ionizing radiation present a fertile field of investigation to the radiobiologist.

COMMENT

Reference to the status of knowledge in 1950 concerning radiation cataract shows that notable progress has been made, though many problems are still unresolved. From a survey of the human cases, such as those of atomic bomb victims, cyclotron victims, and victims of nuclear reactor accidents, it is apparent that 10 to 20 rep of fast neutrons must be regarded tentatively as a sufficient dose to induce lens opacities which may interfere with eyesight. Additional data are needed to determine the cataractogenic x-ray or gamma-ray dose in humans; until such data are forthcoming, it seems wise to consider 500 r of x-rays or gamma rays as potentially dangerous to the human lens.

Variation in susceptibility among species needs further exploration, especially in species not yet so studied, such as dogs and simians. The possibility that dogs are less susceptible to lens damage than other species should be investigated. In mice and rabbits, the cataractogenic dose level for x-rays lies somewhere between 100 and 250 r for acute exposures, and the fast-neutron dose level seems to be between 1 and 10 rep. There are insufficient data on chronic exposures to permit any definite conclusions beyond the expectation that the relative biological effectiveness of x-rays versus fast neutrons will be found to exceed that for acute exposures by a consider-

able factor. The severity of lens damage and the latent period of development are inverse functions of both dose and age. The incidence of lens opacities does not seem to be a critical function of fast-neutron energy. Thermal neutrons in acute doses are about six times as effective in producing visible opacities in mice as are x-rays. Systemic effects have not been shown to be an important contributing cause of radiation cataract; in fact, the evidence to date indicates that radiation cataract is primarily a lens phenomenon. Progress in neutron dosimetry, especially for mixed beams of neutrons and gamma rays, has been made, but this instrumentation is not widely available to radiobiologists.

Cytological and biochemical researches on the lens suggest strongly that the lens epithelium may be the initial site of biological injury, leading eventually to radiation cataract. Clinical observations and cytological data on cellular damage as a result of exposure to ionizing radiation have led to a better understanding of the pathogenesis of radiation cataract. It is postulated that the long latent period between exposure and the development of clinically observable abnormalities at the posterior pole of the lens is the consequence of the slow migration of injured cells from the equator to the posterior pole. Inhibition of cellular division and the occurrence of an overcompensating increase in the mitotic rate after recovery from inhibition have been demonstrated for epithelial cells of the lens in rabbits after exposure to large doses of x-rays; abnormal forms of cellular division and nuclear fragmentation were observable in the epithelial cells of these rabbits.

Metabolic studies on rabbit lenses cultured in vitro show that glutathione and protein are being continuously synthesized from their constituent amino acids. There is no conclusive evidence that initial changes in permeability of the lens or lens capsule immediately after irradiation are contributing factors to lens damage; changes in permeability do accompany the process of opacification. A respiratory enzyme system is active in the lens epithelium but not in the cortex. The lens epithelium appears to have a strictly aerobic type of metabolism, while the cortex and nucleus seem to have a strictly anaerobic type. It is proposed that one of the major functions of the lens epithelium may be to provide energy for metabolism in the cortex and nucleus. Inactivation of the enzyme systems in the epithelium after irradiation may be a contributing factor in mitotic inhibition.

Gray, in a recent survey of radiobiology, has pointed out:

> When all the information concerning mammalian generative tissues is considered, the remarkable fact emerges that the cells which go to form generative tissues, whether in animal or plant, adult or embryo, all require comparable doses of x-irradiation to damage them grossly when they are actively proliferating. It is noteworthy that all these tissues have in common the fact that they are more easily damaged by neutron radiation than by an equal dose of x- or gamma radiation. The relative effectiveness of the two radiations is, in fact, much the same in the different tissues.

It is likely that the relative effects of neutrons and x-rays on the generative tissue of the lens epithelium are also similar to the effects in other generative tissues but that, because of the unique structure of the lens, the toleration dose of ionizing radiation is smaller than in other tissues. When bone marrow, for example, is injured by radiation, the damaged cells may be sloughed off and, after various metabolic changes, removed or excreted from the biological system; eventually, the bone marrow recovers its biological function if the dose of radiation is not overwhelming. The

lens, on the other hand, appears to have a "memory" for cellular damage, so that cells which are abnormal but still viable remain within the lens for life because of the lens capsule and eventually collect around the equator or posterior pole, where they attempt unsuccessfully to differentiate into normal lens fibers. This capacity of the lens to "store up" damaged cells could account for its susceptibility to chronic doses of radiation. In a sense, it becomes a question of how many damaged cells the lens can tolerate before the clinical manifestation known as radiation cataract interferes with vision.

Both x-rays and neutrons cause nuclear damage to proliferating cells, but most of the evidence available suggests that heavily ionizing particles are more efficient in producing nuclear damage than x-rays or gamma rays. On the other hand, there is some reason to believe that x-rays are especially efficient in inactivating enzymes and interfering with metabolic processes, which are often reversible with time. In view of the above observations, it is perhaps not surprising that experiments have shown neutrons to be more effective in producing lens damage than x-rays.

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Annual Reviews

NEURO-OPHTHALMOLOGY

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NEW YORK

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From the Institute of Ophthalmology, Presbyterian Hospital.

VISUAL PATHWAYS

Anatomy.—From an analytical correlation of the homonymous hemianopic field defects, skull x-rays, and surgical observations in 188 cases of penetrating head injuries, Spalding [1] postulates new theories concerning the nerve fiber arrangement within the anterior portion of the optic radiation and in the striate cortex. The interested reader will enjoy the logic of the ideas, but the conclusions should be regarded only as theoretical deductions, since histological studies of necropsy specimens were not made.

Physiology.—Visual field studies should determine not only the peripheral limits but also the sensitivities over the entire area of the field. Two fundamental types of studies are defined according to the threshold measured: (1) The absolute threshold is the minimum intensity of light perceivable against a background of absolute darkness, and (2) the differential threshold is the minimum intensity of light perceivable against an illuminated background. These threshold values vary depending upon the state of light or dark adaptation; but, in general, campimetry in the dark measures the absolute threshold in the dark-adapted eye (scotopic field), and campimetery in the light measures the differential threshold in the light-adapted eye (photopic field).

Bender and Krieger [2] found that some patients who show a homonymous hemianopsia with conventional perimetry (differential threshold field) can perceive and localize a luminous test object in the apparently anopic areas provided the background illumination is absent (absolute threshold field). Increase in the intensity of the background illumination then renders the test object subjectively invisible again. Thus, anopia found by ordinary perimetry is due to inadequate difference in brightness between background and test object

Apparatus.—Harrington [3] describes the use of test objects rendered luminescent with ultraviolet light. Only the test object and the fixation target are visible, thus eliminating visual distraction. This measures the scotopic field. In view of the reports of Bender and Krieger [2] that a field defect may escape detection under scotopic conditions, it is hoped that Harrington will soon report a comparative evaluation of field studies done with his method and with ordinary perimetry.

Methyl Alcohol Blindness.—Benton and Calhoun [4] report a dramatic catastrophe involving 320 persons suffering from symptoms of acute methyl alcohol poisoning. Thirty-seven deaths occurred. The authors draw interesting and important conclusions from their exhaustive clinical observations. Visual symptoms, vary-

1. Spalding, J. M. K.: Wounds of the Visual Pathway: I. The Visual Radiation, J. Neurol., Neurosurg. & Psychiat. **15**:99-109 (May) 1952; Wounds of the Visual Pathway: II. The Striate Cortex, ibid. **15**:169-183 (Aug.) 1952.

2. Bender, M. B., and Krieger, H. P.: Visual Function in Perimetrically Blind Fields, A. M. A. Arch. Neurol. & Psychiat. **65**:72-79 (Jan.) 1951. Krieger, H. P., and Bender, M. B.: Dark Adaptation in Perimetrically Blind Fields, A. M. A. Arch. Ophth. **46**:625-636 (Dec.) 1951. Bender, M. B., and Krieger, H. P.: Background Illumination and the Visual Threshold in Hemianopic Areas, Neurology **3**:102-110 (Feb.) 1953.

3. Harrington, D. O.: Perimetry with Ultraviolet (Black) Radiation and Luminescent Test Objects: A Preliminary Report, A. M. A. Arch. Ophth. **49**:637-642 (June) 1953.

4. Benton, C. D., Jr., and Calhoun, F. P., Jr.: Ocular Effects of Methyl Alcohol Poisoning: Report of a Catastrophe Involving 320 Persons, Tr. Am. Acad. Ophth. **56**:875-885 (Nov.-Dec.) 1952.

ing from blurring to complete blindness, developed 18 to 48 hours after ingestion of the mixture, containing 35% methyl alcohol and 15% ethyl alcohol. All patients who regained and retained normal acuity did so within six days after treatment was begun; if vision did not return to normal within six days, the acuity invariably dropped again to a very low level. The degree of impairment of the pupillary light reflex was of considerable prognostic value. Patients with dilated, fixed pupils usually died; if they lived, they had severe visual loss. Mild degrees of pupillary impairment indicated a more favorable outcome, and normal pupillary responses prognosticated recovery of normal or near-normal acuity. Hyperemia of the optic disk, edema of the disk and peripapillary retina, and retinal venous engorgement were seen, in varying degrees, in 87% of patients. After 30 to 60 days the primary type of optic atrophy developed in the cases of severe visual damage; occasionally, cupping of the disk, simulating glaucomatous cupping, was observed. In the early stages the typical visual field defect was a dense cecocentral scotoma. In others it arched above fixation, sparing central acuity. In some a central scotoma occurred. In most cases the peripheral field was normal but became constricted after two to four months, to involve all, or nearly all, of the visual field.

Methyl alcohol was found in the blood, urine, spinal fluid, and aqueous and vitreous humors of the eye. The carbon dioxide-combining capacity of the blood was normal in 188 patients who probably did not imbibe the poison. In all others the degree of acidosis was an invaluable guide to diagnosis, therapy, and prognosis. The most effective treatment consists of intensive and prolonged alkalization. Histological examinations of six eyes enucleated 6 to 18 hours after death revealed changes consistent with postmortem degeneration.

Optic Neuritis.—Realizing that sudden remissions can occur in optic neuritis without treatment and that final conclusions are not warranted from one case, Smith,[5] nevertheless, feels that corticotropin given intravenously materially contributed to the return of normal vision in a patient with bilateral optic neuritis. The vision had not improved under oral treatment with cortisone.

Hereditary Optic Atrophy.—Leber's type of optic atrophy may appear alone or in combination with other hereditary degenerative diseases, including the cerebellar ataxias, spastic paraplegia, peroneal muscular atrophy, hypertropic neuritis, and auditory nerve atrophy. Some authors believe that Leber's optic atrophy is a separate disease entity. From an analytical review of the literature, Bereday and Cobb[6] conclude, as do many others, that it is an integral part of a hereditary degenerative disease of the nervous system.

Syphilitic Optic Atrophy.—Every ophthalmologist and neurologist should study the excellent monograph "Syphilitic Optic Atrophy," by Bruetsch.[7] Eighty patients with neurosyphilis were observed clinically, and, at necropsy, their visual pathways were examined histologically from the retina to the occipital visual cortex. Critical analysis of these data and of the literature enabled the author to contribute new

5. Smith, E. L.: Intravenous Use of Corticotropin in Optic Neuritis, A. M. A. Arch. Ophth. **49**:303-312 (March) 1953.

6. Bereday, M., and Cobb, S.: Relation of Hereditary Optic Atrophy (Leber) to Other Familial Degenerative Diseases of Central Nervous System, A. M. A. Arch. Ophth. **48**:669-680 (Dec.) 1952.

7. Bruetsch, W. L.: Syphilitic Optic Atrophy, Springfield, Ill., Charles C Thomas, Publisher, 1953.

information, to confirm previous observations, and to refute conflicting theories concerning every phase of this subject. Most attention is devoted to pathogenesis. He rejects the theory of primary parenchymatous degeneration of nerve fibers but convincingly confirms the concept of Léri,[8] who, in 1904, first showed that the fundamental lesion always consists of an interstitial neuritis. The inflammation always begins as a syphilitic basilar meningitis affecting the intracranial portion of the optic nerves or the optic chiasm; the meningitis may escape gross inspection but is recognized microscopically. Interstitial neuritis spreads toward the inner fibers and may extend posteriorly, into the optic tracts, or anteriorly, into the intracanalicular portion of the optic nerves. The anterior two-thirds of the intraorbital portion of the optic nerve is not involved. To produce optic atrophy, the meningitis must be of severe intensity and of long duration, with production of demyelination. The slow degeneration of nerve fibers is secondary to the inflammatory reaction and is not due to mechanical pressure or traction produced by arachnoiditic adhesions or bands. The pathogenesis is similar in isolated syphilitic optic atrophy, meningovascular syphilis, dementia paralytica, and tabes.

Blindness was inevitable before the introduction of malaria therapy and penicillin and is still inevitable unless the neuritic process is recognized in its incipient stage. Early diagnosis—of paramount importance— is made by careful visual field studies. Almost any type of field defect can occur, but the commonest is an irregular depression of the peripheral field. Central scotomata are less common. Field defects can precede the appearance of optic disc pallor, and color of the disc does not always parallel nerve function; therefore, the tangent screen examination is more important in early diagnosis than is the ophthalmoscopic study. Prognosis is more favorable when central vision is not impaired. Brilliant results are being attained with malaria and penicillin therapy if the neuritic process is diagnosed early, but years will be required for the development and evaluation of modern therapeutic agents.

Twenty-three patients with progressive syphilitic optic nerve atrophy were treated with large doses of penicillin for about four years by Benton and Harris.[9] The authors conclude that penicillin is effective in arresting further visual loss if the pretreatment visual acuity is 20/50 or better in one or both eyes, but that further loss of vision usually results if the initial acuity is less than 20/50 in both eyes.

Compression of Optic Nerve Intracranially.—Increasing attention is directed toward the importance of visual impairment due to lesions which compress the intracranial portion of the optic nerve. Such lesions are usually misdiagnosed as retrobulbar neuritis.

Hauser and Gass [10] relate the case of a 34-year-old woman, nearly blind in the left eye, which had deviated inward since childhood. She complained of rapidly

8. Léri, A.: Étude de la rétine dans l'amaurose tabetique, Nouv. iconog. Salpêtrière **17**:304-310, 1904; Étude du nerf optique dans l'amaurose tabetique, ibid. **17**:358-375, 1904.

9. Benton, C. D., Jr., and Harris, J. F.: Syphilitic Optic Nerve Atrophy Treated with Penicillin: Observations 2 to 6 Years After Treatment, A. M. A. Arch. Ophth. **48**:449-454 (Oct.) 1952.

10. Hauser, M. J., and Gass, H.: Optic Nerve Pressure by Aneurysm Relieved by Decompression of Optic Nerve: Report of a Case, A. M. A. Arch. Ophth. **48**:627-631 (Nov.) 1952.

decreasing vision in the right eye for the preceding 10 days. During the next four days the vision decreased from 20/50, with a superior field defect, to complete loss of light perception. Papilledema of 1 D. in the right eye was the only other ocular sign. Physical and neurological examinations, x-rays of the skull, cerebral arteriography, and pneumonencephalography revealed no abnormality. Despite absence of significant findings, the rapid development of blindness in the only useful eye prompted an exploratory craniotomy. When the optic canal was unroofed, an aneurysmal dilatation at the junction of the internal carotid and the ophthalmic artery on the right was revealed. The authors state that treatment consisted only of decompression of the optic nerve, since trapping the aneurysm with clips placed on the carotid artery on each side of the aneurysm would deprive the eye of its blood supply through the ophthalmic artery, with great risk to the patient's vision. An excellent result, of 20/30 vision with only an inferior nasal field defect was obtained, and this has been maintained for two years. This case instructively demonstrates the advisability of exploratory craniotomy in desperate cases, despite normal arteriograms.

It should be recalled that blindness does not result, even though the ophthalmic artery is isolated by the trap operation, in which the internal carotid artery is isolated by proximal ligation in the neck and by distal ligation, intracranially, beyond the origin of the ophthalmic artery. This is due to the rich and adequate collateral circulation existing between the ophthalmic artery and the homolateral, as well as the contralateral, external carotid artery. This collateral supply was shown experimentally by Elschnig,[11] in 1893, and by Walsh and King,[12] in 1942, and, clinically, by Dandy[13] in 1938, and by numerous other neurosurgeons since.

Patients presenting the clinical picture of retrobulbar neuritis in one eye should always be suspected of having a meningioma of the anterior clinoid process. Uihlein and Weyand[14] report 52 such cases, in which the average duration of symptoms before the diagnosis was made was four years; 17 deaths accounted for a 32% postoperative mortality in this group. The authors stress the importance of early diagnosis and early surgical excision, not only to prevent blindness in the other eye but to lower the mortality.

In discussing the involvement of the ocular apparatus during the course of systemic lymphomatous disease, Feinstein and Krause[15] report a rare case, that of a man aged 31 who had onset of blindness and primary optic nerve atrophy in the left eye. Craniotomy revealed a lymphosarcoma situated beneath the optic chiasm, compressing both optic nerves.

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11. Elschnig, A.: Über den Einfluss der Verschlusses der Arteria ophthalmica und der Carotis auf das Sehorgan, Arch. Ophth. **39**:151-177, 1893.

12. Walsh, F. B., and King, A. B.: Ocular Signs of Intracranial Saccular Aneurysms; Experimental Work on Collateral Circulation Through the Ophthalmic Artery, Arch. Ophth. **27**:33 (Jan.) 1942.

13. Dandy, W. E.: Intracranial Aneurysm of Internal Carotid Artery Cured by Operation, Ann. Surg. **107**:654-659 (May) 1938.

14. Uihlein, A., and Weyand, R. D.: Meningiomas of Anterior Clinoid Process as a Cause of Unilateral Loss of Vision: Surgical Considerations, A. M. A. Arch. Ophth. **49**:261-270 (March) 1953.

15. Feinstein, A. R., and Krause, A. C.: Ocular Involvement in Lymphomatous Disease, A. M. A. Arch. Ophth. **48**:328-337 (Sept.) 1952.

Chiasmal Syndrome.—Weyand, Craig, and Rucker [16] report five cases of involvement of the optic chiasm by unusual lesions: nasopharyngeal carcinoma, syphilis, lipid reticuloendotheliosis, simple cyst, and fibrous dysplasia.

Visual Obscurations.—Ethelberg and Jensen [17] discuss obscurations which occurred in 140 of 500 consecutive cases of intracranial tumors. Obscurations are defined as sudden and rapidly transient attacks of impaired vision affecting both eyes, varying from blurring of vision to complete blackouts, followed by immediate and complete recovery of vision. They vary as regards the area of field involved; photopsiae may occur before, during, or after the obscuration. In some patients the obscurations followed a sudden change in the position of the head or of the body. Their occurrence was independent of the location and nature of the primary space-occupying lesion, but was more frequent the more the supratentorial pressure was elevated. The authors assume that the obscurations are due to transient interference with the circulation through both posterior cerebral arteries when these vessels come close to the free edge of the tentorium during the initial phase of the displacement and herniation of the mesial parts of the temporal lobe into the tentorial incisure. Rapidly transient changes in arterial circulation affecting extensive areas of the temporal lobes and occipital lobes are assumed to cause the attacks of hallucinations in some cases. Displacement and herniation of the midbrain may produce circulatory changes affecting not only mesencephalic structures, but diencephalic structures as well, thus accounting for the attacks of changes in muscular tone and transient unconsciousness which occasionally develop. Attacks of obscurations, combined with chalastic or hypertonic fits, and of impaired consciousness indicate an impending fatal herniation of parts of the brain into the tentorial incisure, and immediate measures should be taken to confirm or deny a diagnosis of a space-occupying intracranial lesion.

Visual Hallucinations.—Parkinson, Rucker, and Craig [18] report that 12 of 50 patients harboring occipital lobe tumors had visual hallucinations. They conclude that their cases are compatible with the concept that the hallucinations, when present with lesions limited to the occipital lobe, are of the unformed variety, are observed in the opposite homonymous visual field, and are limited usually to the area of a field defect.

Bilateral Occipital Lobe Infarctions.—Lawrence [19] reports the instructive case of a man aged 47 who complained of progressive loss of vision in each eye during the previous 10 days. The vision in each eye was reduced to light perception at the periphery, with a central scotoma larger than 20 degress in each visual field; the pupils were equal and reacted normally, and the fundi were normal. On the basis of these signs a clinical diagnosis of bilateral retrobulbar neuritis was made.

16. Weyand, R. D.; Craig, W. M., and Rucker, C. W.: Unusual Lesions Involving the Optic Chiasm, Proc. Staff Meet., Mayo Clin. **27**:505-511 (Dec. 3) 1952.

17. Ethelberg, S., and Jensen, V. A.: Obscurations and Further Time-Related Paroxysmal Disorders in Intracranial Tumors: Syndrome of Initial Herniation of Parts of the Brain Through the Tentorial Incisure, A. M. A. Arch. Neurol. & Psychiat. **68**:130-149 (July) 1952.

18. Parkinson, D.; Rucker, C. W., and Craig, W. M.: Visual Hallucinations Associated with Tumors of the Occipital Lobe, A. M. A. Arch. Neurol. & Psychiat. **68**:66-68 (July) 1952.

19. Lawrence, G. A.: Bilateral Occipital-Lobe Infarction Simulating Retrobulbar Neuritis: Report of Case Terminating Fatally During Use of Corticotropin, A. M. A. Arch. Ophth. **48**:602-604 (Nov.) 1952.

Except for slight hypertension (140/90), the physical and neurological examinations, x-rays of the skull, and laboratory studies revealed nothing abnormal. After one week of treatment with parenteral administration of corticotropin, there occurred the simultaneous onset of paralysis and numbness of the left arm and leg, weakness of the left side of the face, ptosis of the left upper eyelid, and paralysis of the left internal rectus muscle. A diagnosis of thrombosis in the region of the pons was made, and the patient died six days later. Autopsy revealed fairly severe arteriosclerosis of the arteries at the base of the brain. The optic nerves and chiasm were normal, but infarctions involved the posterior pole and medial aspect of both occipital lobes.

The authors suggest that the corticotropin may have been responsible for the final thromboses in the brain stem, in view of recent reports on the hypercoagulability of the blood associated with corticotropin therapy. The case is also presented as an instance of bilateral central scotoma due to suprachiasmal (occipital lobe) rather than prechiasmal (optic nerve) disease.

This paper serves to remind us again that severe bilateral impairment of central vision is not always due to a bilateral optic nerve lesion, but that lesions in both occipital poles must be considered in the localization of the disease process. It seems justifiable to remark that the presence of normal pupillary reactions, associated with severe bilateral central visual impairment, should lead one to suspect that the lesions are in the occipital lobes. In severe bilateral optic neuritis the pupillary reactions to light are markedly impaired or completely lost, whereas in cortical blindness the pupillary reactions are characteristically normal.

It is not stated which arteries were occluded. This clinical picture contrasts strikingly with that observed when bilateral occlusion of the posterior cerebral artery produces bilateral homonymous hemianopsia with preservation of central acuity, due to the sparing of each macula.

Wagman [20] reports the rare case of a man aged 77, without preceding ocular symptoms, who had sudden onset of total and permanent blindness, attributed to bilateral infarction of the visual cortex. No objective neurological or ocular signs were present. The features were typical of cortical blindness: The pupils reacted to light; the optic disks remained normal, and voluntary gaze movements were normal. Perimetrically, the defect was a simultaneous bilateral homonymous hemianopsia without sparing of macular vision. Autopsy was not performed, but it was believed that there was thrombosis of each posterior cerebral artery.

General Considerations.—In a comprehensive monograph, Dubois-Poulsen [21] discusses all aspects of the visual field in their most modern dress. Thirteen chapters are devoted to physiology; 11 chapters describe examination techniques and the field changes observed in diseases of the entire visual pathway. An English translation of this great work would be a truly valuable contribution to ophthalmic literature.

20. Wagman, O. H.: Sudden Blindness Due to Intracranial Vascular Accident: Simultaneous Bilateral Homonymous Hemianopia (Without Sparing of the Macula) Following Infarction of the Visual Cortex, New England J. Med. **247**:7-10 (July 3) 1952.

21. Dubois-Poulsen, A.: Le champ visuel: Topographie normale et pathologique de ses sensibilités, Paris, Masson & Cie, 1952.

The etiology and clinical features of the various types of hemianopsia are discussed in a lengthy article by Bonnet.[22]

Chamlin [23] reemphasizes several points concerning the field changes which are helpful criteria in the recognition and differential diagnosis of papilledema, optic atrophy, optic neuritis, chiasmal interference, and homonymous hemianopsia.

Burns, Hanley, Pietri, and Welsh [24] studied the usefulness of the spectacle mirror in six cases of homonymous hemianopsia. In left hemianopsia, for example, the images of objects on the left side appear to be situated and superimposed upon the objects on the right side. All six patients experienced confusion and disappointment.

PAPILLEDEMA

Diagnosis.—The search continues for a sign pathognomonic of true papilledema in its earliest stage. Chamlin and Davidoff [25] discuss the clinical features and differential diagnosis of papilledema. They stress (and rightfully) that the dioptric elevation of the disk is unreliable as a sign of the presence of papilledema or as an index of an increase or a decrease in the extent of papilledema. This important point is not generally appreciated. No satisfactory explanation accounts for the dissimilar appearances of the disks in different persons who have equal degrees of increased intracranial pressure.

The diagnosis of papilledema commonly involves differentiation from pseudopapilledema, drusen of the optic disc, and optic neuritis. Ophthalmoscopic appearances may not differentiate with certainty true papilledema and pseudopapilledema, but the authors believe that the blind spot is always normal in size in pseudopapilledema, whereas they have observed abnormal enlargement of the blind spot in true papilledema even before it is evident with the ophthalmoscope. On the basis of this belief, they emphasize the importance of accurately measuring the size of the blind spot with a tangent rule, and they describe in detail their technique for determining whether or not a blind spot is pathologically enlarged.

Having observed enlarged blind spots in pseudopapilledema and in ophthalmoscopically normal discs, I cannot confirm the great value assigned by the authors to the enlarged blind spot in the definite diagnosis of incipient papilledema.

Ophthalmoscopic features do not suffice to differentiate optic neuritis and papilledema. Field studies are indispensable. In papilledema the blind spot is enlarged; this defect becomes less dense as it extends away from the blind spot. In optic neuritis the central scotoma is densest at the fixation area and becomes less dense as it extends away from the fixation area.

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22. Bonnet, P.: Valeur séméiologique de l'hémianopsie, J. méd. Lyon **33**:587-624 (June 20) 1952.

23. Chamlin, M.: Visual Field Studies in Neurosurgical Problems, Eye, Ear, Nose & Throat Month. **31**:415-422 (Aug.) 1952.

24. Burns, T. A.; Hanley, W. J.; Pietri, J. F., and Welsh, E. C.: Spectacles for Hemianopia: A Clinical Evaluation, Am. J. Ophth. **35**:1489-1492 (Oct.) 1952.

25. Chamlin, M., and Davidoff, L. M.: Papilledema: Its Differential Diagnosis, with Special Reference to Minimal Testing of the Blind Spot at 2 Meters, A. M. A. Arch. Neurol. & Psychiat. **68**:213-232 (Aug.) 1952.

Chamlin and Davidoff [26] report what they consider to be the first case in which drusen of the optic discs were observed clinically, photographed in colors, and studied pathologically after the patient's death.

Williamson-Noble [27] discusses factors responsible for the venous pulsation on the optic disc. His significant contribution, however, concerns the clinical significance of venous pulsation in relation to the height of the intracranial pressure. In 1939 Brown [28] stated that venous pulsation, spontaneously present or appearing when minimal pressure is applied to the eyeball, indicates that the intracranial pressure is not abnormally elevated. This appeared to be the pathognomonic sign of papilledema—sought by physicians for years. Williamson-Noble believes that the test is not valid, since he has observed venous pulsation, spontaneously present or elicited with light pressure on the globe, in patients showing unmistakable papilledema and proved to have increased intracranial pressure. From personal observations, I confirm these statements of Williamson-Noble concerning the unreliability of this phenomenon in the diagnosis of increased intracranial pressure. In some cases venous pulsation appears to be absent, but not always.

Meningeal Hydrops.—Meningeal hydrops is discussed by Giller and Cogan [29] in an excellent paper, deserving to be read in the original. The ophthalmologist occasionally encounters an apparently healthy patient who complains of headaches and blurred vision. Examination reveals normal visual acuity, bilateral papilledema, and enlarged blind spots with essentially normal peripheral visual fields. An intracranial space-occupying lesion is suspected, but neurological signs are absent or minimal. Skull x-rays and the electroencephalogram are normal. Lumbar puncture reveals an abnormally elevated cerebrospinal fluid pressure, but the fluid is clear, is usually free of cells, and has a normal protein content. Ventriculography shows no asymmetry or dilatation of the ventricles; rarely, the ventricles appear slightly smaller than normal. When one is confronted with this group of findings, the possibility of a tumor in a silent area of the brain must be considered. Observations at regular intervals, however, reveal gradual improvement in the symptoms and signs over periods varying from several weeks to a few years. The prognosis is good.

Seven cases are reported. One patient died, and necropsy revealed thrombosis of the posterior half of the superior longitudinal sinus. Giller and Cogan believe that the commonest proved cause of this condition is thrombosis of the dural venous sinuses. In other cases in the literature the condition has been attributed to, or associated with, otitis media, menstrual edema, the postpartum state, and head injuries. Meningeal hydrops is also referred to in the literature as pseudotumor cerebri, otitic hydrocephalus, serous meningitis, arachnoiditis, intracranial hypertension of unknown cause, and toxic hydrocephalus.

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26. Chamlin, M., and Davidoff, L. M.: Drusen of the Optic Nervehead: Ophthalmoscopic and Histopathologic Study, Am. J. Ophth. **35**:1599-1605 (Nov.) 1952.

27. Williamson-Noble, F. A.: Venous Pulsation, Tr. Ophth. Soc. U. Kingdom **72**:317-326, 1952.

28. Brown, T. H.: Cerebro-Spinal Disease and Its Relation to the Optic Nerve, Tr. Ophth. Soc. U. Kingdom **59**:861-993, 1939.

29. Giller, H., and Cogan, D. G.: Papilledema as the Outstanding Sign in Meningeal Hydrops, A. M. A. Arch. Ophth. **48**:557-566 (Nov.) 1952.

Unusual Absence.—Hepburn [30] reports an unusual case of a man aged 25 who had pain and swelling in the right suboccipital region, vomiting, and depression. The patient's discomfort and lack of cooperation precluded thorough examinations and x-ray studies, but it was observed that there was no papilledema in either eye. Autopsy revealed bronchogenic carcinoma with multiple cerebral metastases and spina bifida occulta of the second cervical vertebra. A patent channel lined with meninges communicated with the spinal canal. The explanation offered is that the increased intracranial pressure expanded the meningocele in the neck, thus decompressing the cranial cavity and preventing the development of papilledema.

PUPILS

Experimental Studies.—Lowenstein, Murphy, and Loewenfeld [31] studied the pupillary light reflex pathways in cats by pupillography. Their anatomical and physiological conclusions, though interesting, are not applicable to man.

Syphilis.—From pupillographic studies of four cases of syphilis with negative serologic reactions of the spinal fluid and no other neurological signs, Jaffe [32] states that there are various early alterations in the pupillary reflexes which are invisible to the naked eye and are detected only by pupillography. Contrary to general thought, syphilitic invasion of the brain is not a late manifestation but occurs early, usually during the first year of the disease. Also, the reaction to near vision is not normal, as is commonly described, but is actually impaired, although to a less degree than is the reaction to light.

Mechanism of Pupillary Changes.—With lucid text and excellent photographs of dissections, Sunderland [33] describes one mechanism responsible for the appearance of pupillary signs, unaccompanied by disturbances of the extraocular muscle functions, in intracranial lesions. The tentorial gap is bounded posteriorly by the cerebral peduncle, anteriorly by the dorsum sellae, and laterally by the margin of the tentorium. The oculomotor nerve emerges from the mesencephalon on the medial side of the cerebral peduncle; as it passes through this gap to reach the roof of the cavernous sinus, it is in intimate relation superiorly with the posterior cerebral and posterior communicating arteries, inferiorly with the superior cerebellar artery, and laterally with a portion of the uncal region of the temporal lobe which normally extends for a short distance over the tentorial margin. Sunderland and Hughes [34] had previously demonstrated that the parasympathetic pupilloconstrictor fibers are concentrated over the superior arc of the oculomotor nerve in this region and, therefore, that pressure upon the superior surface of this portion of the oculomotor nerve produces pupillary disturbances. Such pressure can be produced by

30. Hepburn, W. D. S.: Multiple Cerebral Metastases Without Papilloedema: Cervical Meningocoele as a Possible Decompressing Mechanism, Confinia neurol. **13**:1-6, 1953.

31. Lowenstein, O.; Murphy, S. B., and Loewenfeld, I. E.: Functional Evaluation of the Pupillary Light Reflex Pathways: Experimental Pupillographic Studies in Cats, A. M. A. Arch. Ophth. **49**:656-670 (June) 1953.

32. Jaffe, N. S.: The Pupil in Syphilis, Am. J. Ophth. **36**:493-500 (April) 1953.

33. Sunderland, S.: Mechanism Responsible for Changes in the Pupil Unaccompanied by Disturbances of Extra-Ocular Muscle Function, Brit. J. Ophth. **36**:638-644 (Nov.) 1952.

34. Sunderland, S., and Hughes, E. S. R.: The Pupillo-Constrictor Pathway and the Nerves to the Ocular Muscles in Man, Brain **69**:301-309 (Dec.) 1946.

anomalies or aneurysms of the adjacent arteries and by herniation of the uncus over the edge of the tentorium. Tentorial herniations can develop as the result of various expanding intracranial lesions.

Miosis occurs initially and transiently if the constrictor fibers are irritated; this is followed by mydriasis if the fibers are later paralyzed. Paralytic mydriasis often develops without an initial miosis. The pupillary signs may be absent if the pressure has developed slowly and are more likely to occur if the pressure on the nerve has developed rapidly. Further increases in pressure paralyze the remaining somatic fibers of the oculomotor nerve, producing disturbances in the function of the extraocular muscles.

Pupillary Changes Accompanying Extradural Hemorrhage.—Mydriasis is a vital sign in extradural hemorrhage. Sunderland and Bradley [35] describe its pathogenesis and clinical features in detail. Previous theories had suggested that the lesion is located centrally, in the third nucleus, or in the third nerve, either at the greater wing of the sphenoid bone or in the superior orbital fissure. On four necropsy specimens the authors demonstrate that the third nerve is involved in the tentorial gap as it passes anteriorly from the medial side of the cerebral peduncle toward the cavernous sinus. Extradural hemorrhage compresses the brain, producing a herniation of the temporal lobe over the tentorial margin. The herniation first impinges upon the ipsilateral third nerve and then displaces the brain stem, causing both third nerves to be stretched, and later to be angulated by the posterior cerebral arteries. The pupilloconstrictor fibers, concentrated in the superior portion of the nerve, are affected earlier than are the somatic fibers, innervating the extraocular muscles and the levator muscle of the eyelid. Irritation produces miosis; later, paralysis causes mydriasis.

After the head injury pupillary signs appear early, within a few minutes, and progress rapidly, within 12 hours, to a state of bilateral dilatation and fixation to light, in the following sequence: 1. Ipsilateral miosis appears, lasting only a few minutes; this is often missed unless the pupils are examined at frequent intervals. At this stage one must differentiate carefully between ipsilateral miosis and apparent mydriasis on the normal (contralateral) side; the larger (normal) pupil will react to light. 2. The ipsilateral pupil slowly dilates and becomes fixed to light after 1 to 12 hours. This dilated and fixed pupil is one of the most constant and reliable lateralizing signs and is generally well known. 3. The contralateral pupil constricts. 4. The contralateral pupil then becomes dilated and fixed. Within approximately 12 hours after injury both pupils are dilated and fixed.

Pupillary signs are delicate indicators of the progress of the herniation and are of grave prognostic significance. Operation is urgent—within minutes—even if only one pupil is dilated and fixed; survival is unlikely if one or both pupils are dilated and fixed for longer than 30 minutes. After decompression, death is almost certain if the pupillary state persists, whereas the patient will probably live if pupillary activity returns within a few minutes. If a second hemorrhage occurs after successful decompression, the pupillary signs rapidly recur, again indicating the urgency for a second operative decompression.

35. Sunderland, S., and Bradley, K. C.: Disturbances of Oculomotor Function Accompanying Extradural Hemorrhage, J. Neurol. Neurosurg. & Psychiat. **16**:35-46 (Feb.) 1953.

Involuntary ocular movements in the comatose patient, and voluntary movements in the conscious patient, reveal that the extraocular muscles and the levator muscle of the upper eyelid are affected on the ipsilateral side. These somatic fibers fail later than do the ipsilateral pupillary fibers. If hemiplegia occurs, it is usually contralateral, owing to compression of the ipsilateral cerebral peduncle; occasionally, however, the opposite cerebral peduncle is compressed, producing ipsilateral hemiplegia—a false lateralizing sign. In this case, lateralization of the hemorrhage becomes even more difficult if the eyes have not been examined before both pupils are dilated and fixed. Invaluable aid may then be obtained by noting that the ipsilateral eye is stationary, whereas the contralateral eye moves and roves about. During recovery the pupillary signs reappear rapidly; the ocular movements return more slowly, and the levator muscle recovers last. It is not known why pupillary signs do not develop in all cases of extradural hemorrhage.

EXTRAOCULAR MUSCLES

Proprioception.—Ludvigh [36] presents convincing experimental evidence that the muscle spindles found in the extraocular muscles by Daniel do not effectively contribute to a position sense of the eye.

Control of Ocular Movements.—In this paper, Ludvigh [37] advances the hypothesis that the ocular movements of fixation and pursuit are controlled by parametric feedback provided by the muscle spindles. This mechanism is similar to that which Gellhorn describes in skeletal muscle. The discussion of the material in this paper is highly complex.

Progressive External Ophthalmoplegia.—Slowly progressive external ophthalmoplegia beginning in adult life is commonly termed "chronic progressive nuclear ophthalmoplegia." The histopathological picture of a biopsy specimen was first described by Fuchs [38] in 1890; he concluded that the disease is myopathic, and not nuclear, in nature. Subsequent authors [39] have reported evidence to confirm this opinion. No satisfactory evidence that the nuclei are involved has ever been reported. The disease may affect skeletal muscles (progressive muscular dystrophy) or the extraocular muscles (progressive dystrophy of the external ocular muscles) or both; the lesions appear identical in all muscles. Beckett and Netsky [40] report the first case of ocular myopathy in which both the central nervous system and the ocular muscles were examined at necropsy. Mild ptosis and ophthalmoplegia began in a white man during his 20's and gradually progressed to a final stage of marked bilateral ptosis and complete external ophthalmoplegia. The patient died at the age of 68. Typical pathological changes of dystrophy were observed in the ocular muscles, but the cells of the oculomotor and abducens nuclei were normal in number and appearance. This contribution is valuable, for it presents definite evidence

36. Ludvigh, E.: Possible Role of Proprioception in the Extraocular Muscles, A. M. A. Arch. Ophth. **48**:436-441 (Oct.) 1952.

37. Ludvigh, E.: Control of Ocular Movements and Visual Interpretation of Environment, A. M. A. Arch. Ophth. **48**:442-448 (Oct.) 1952.

38. Fuchs, E.: Über isolirte doppelseitige Ptosis, Arch. Ophth. **36**:234-259, 1890.

39. Kiloh, L. G., and Nevin, S.: Progressive Dystrophy of the External Ocular Muscles (Ocular Myopathy), Brain **74**:115-143 (June) 1951.

40. Beckett, R. S., and Netsky, M. G.: Familial Ocular Myopathy and External Ophthalmoplegia, A. M. A. Arch. Neurol. & Psychiat. **69**:64-72 (Jan.) 1953.

against the nuclear theory of the disease and, at the same time, adds support to the idea of its myopathic nature. The authors state that ocular myopathy should be regarded not as a separate disease entity, but as a variant in the localization of the dystrophic process.

Congenital Ocular Motor Apraxia.—A few cases of acquired ocular motor apraxia have been reported, but the first description of the congenital variety has been contributed by Cogan.[41] In both types there is a loss of willed movements of the eyes (in response to command, attraction, or volition) with retention of random movements not directly related to the will. The diagnostic characteristic of the congenital type is a curious jerky compensatory head movement. Since the eyes cannot be turned toward an object, for example, to the left, the head is turned to the left, but this movement elicits the vestibular reflex, causing the eyes to deviate even farther to the right with respect to the head. In order that the eyes may fixate on the object, the head must be turned considerably farther to the left, thus producing the characteristic overshoot. Once the eyes fixate on the object, the head returns to the position directed toward the object. This entire cycle occurs in less than one second. Horizontal movements only are involved; vertical movements are normal. The peculiar head movements, the inability to turn the eyes, or the apparent blindness is the presenting complaint of the parents. No other ocular, neurological, or physical abnormalities were found in the four patients personally studied by Cogan. The only real handicaps are those encountered in reading and in making sharp turns in walking. The cause and pathogenesis are unknown. The condition, curiously, has not been seen in adults.

This syndrome must be differentiated from other disturbances, usually referred to as pseudo-ophthalmoplegia. In acquired ocular motor apraxia both the eye and the head movements are affected and the jerky compensatory movement is absent. In the Roth-Bielschowsky syndrome the vertical movements are affected and there are signs of pseudobulbar palsy. In simple palsies of conjugate gaze the random movements are lost or are decreased to a greater extent than are the willed movements.

Diagnosis of Midbrain Lesion in a Comatose Patient.—In the conscious normal person caloric stimulation with cold water produces nystagmus to the opposite side, whereas in the comatose patient it causes tonic conjugate deviation of both eyes toward the ipsilateral side if the vestimulo-ocular pathways in the medial longitudinal bundle are intact. Klingon [42] reports the case of a comatose patient in whom caloric stimulation with cold water caused the ipsilateral eye to abduct but failed to produce adduction of the contralateral eye. By this demonstration of internuclear ophthalmoplegia, he diagnosed a lesion of the medial longitudinal bundle. Demyelinating lesions were revealed in the brain stem at necropsy.

Recurrent Ophthalmoplegia.—Koistinen [43] reports the case of a woman aged 38 with recurrent ophthalmoplegia, preceded by headaches. Neurological examination

41. Cogan, D. G.: A Type of Congenital Ocular Motor Apraxia Presenting Jerky Head Movements, Tr. Am. Acad. Ophth. **56**:853-862 (Nov.-Dec.) 1952; Am. J. Ophth. **36**:433-441 (April) 1953.

42. Klingon, G. H.: Caloric Stimulation in Localization of Brain-Stem Lesions in a Comatose Patient, A. M. A. Arch. Neurol. & Psychiat. **68**:233-235 (Aug.) 1952.

43. Koistinen, A.: Recurrent Ophthalmoplegia and Unilateral Papilloedema in a Case of Hyperostosis Frontalis Interna, Acta ophth. **30**:421-428, 1952.

revealed only pareses of the right third nerve and right trochlear nerve and 5 D. of papilledema in the left eye. X-rays showed hyperostosis frontalis interna, a new-bone formation which involves the inner table of the frontal bone and the orbital portion of the frontal bone. It is theorized that narrowing of the sphenoidal fissure produces venous congestion, with resulting pressure upon the cranial nerves. The conclusion is not convincing.

Ophthalmoplegic Migraine.—Ophthalmoplegic migraine is a syndrome characterized by severe hemicrania associated with recurrent ipsilateral ophthalmoplegia. The headache is severer than usual and is a true hemicrania. The ophthalmoplegia occurs during or after the hemicrania and involves the ipsilateral oculomotor nerve; rarely, the trochlear or abducens nerve is affected. The paralysis becomes more marked with successive attacks until a permanent unilateral oculomotor ophthalmoplegia finally results.

The presently accepted mechanism of simple ophthalmic migraine is that the preheadache phenomena are due to constriction of the cerebral vessles, with resulting decrease in cerebral volume; the ensuing headache is due to dilatation of the vessels of the scalp and dura and is accompanied by an increase in cerebral volume. The five necropsy reports in the literature have failed, however, to explain the pathogenesis of ophthalmoplegic migraine.

Since Meyer,[44] in 1920, first described herniation of the uncus of the temporal lobe over the tentorial margin, numerous autopsy studies have confirmed the belief that the lateralizing value of unilateral dilatation of the pupil in unilateral space-occupying lesions is due to pressure of the herniated uncus on the ipsilateral third nerve. In presenting a new theory of the pathogenesis of ophthalmoplegic migraine, Harrington and Flocks [45] emphasize that clinical, pathological, anatomical, and experimental evidence demonstrates that the herniation is due to a relative increase in pressure in the ipsilateral half of the cranial cavity. It is the unilaterality of this cerebral edema which explains the lateralizing value of pupillary dilatation. This is often a transient and reversible process. The herniation is not simply the result of generalized increase in intracranial pressure; this more frequently produces unilateral or bilateral abducens nerve palsy.

The authors report the case of a man, aged 50, who had six attacks of right hemicrania associated with transient paralysis of the right third nerve over a 16-day period. They observed four of these attacks. The patient was sitting up for visual field studies when the onset began, with extreme headache on the right side, loss of attention and ability to respond to command, pallor and cold sweat, and loss of urinary sphincter control. In one or two minutes the right pupil gradually dilated, followed by complete paralysis of the entire right oculomotor nerve. Six minutes after the onset of the attack ptosis of the right lid was complete. The patient was then placed in a horizontal position of rest; and after only five minutes, the hemicrania and the ophthalmoplegia disappeared completely, the patient was alert and cooperative, and the skin was normal in color and free from perspiration. Each attack appeared to be precipitated by changes in the patient's position. The last

44. Meyer, A.: Herniation of the Brain, Arch. Neurol. & Psychiat. **4**:387-400 (Oct.) 1920.

45. Harrington, D. O., and Flocks, M.: Ophthalmoplegic Migraine: Pathogenesis: Report of Pathological Findings in a Case of Recurrent Oculomotor Paralysis, A. M. A. Arch. Ophth. **49**:643-655 (June) 1953.

attack was not reversible; the headache continued, and the ophthalmoplegia persisted. Suspecting an intracranial aneurysm, they performed an arteriographic study, revealing a tumor in the right frontal lobe. The patient died a few hours later. Necropsy revealed a bronchogenic carcinoma of the lung with one metastatic lesion in the right frontal lobe and another in the right parietal lobe. There was a pronounced herniation of the right hippocampal gyrus over the tentorial edge, with pressure on, and stretching of, the right oculomotor nerve. Hemorrhages into the brain stem accounted for death.

The hemicrania of ophthalmoplegic migraine is quite different from ordinary migraine; it is severer, of longer duration, and definitely localizable, being trigeminal in distribution. This type is due to the uncal herniation pressing upon the branches of the trigeminal nerve. The homonymous scintillating scotomata, hallucinations, and hemianopsia are due to ischemia of the occipital lobe resulting from compression of the posterior cerebral artery. Hemianopsia becomes permanent if infarction results. Contralateral transient hemiplegia and paresthesias are due to compression of the cerebral peduncle.

Harrington and Flocks conclude that the clinical picture of ophthalmoplegic migraine, in all its protean forms, is produced by herniation of the temporal lobe compressing the posterior cerebral artery, cerebral peduncle, and the several cranial nerves, and that the herniation is secondary to a relative increase in cerebral pressure and edema resulting from physiological or pathological changes in the volume of the cranial contents.

Brain Swelling.—Atkinson [46] contributes a scholarly presentation of cerebral swelling, discussing its physiology, pathology, clinical symptoms and signs, differential diagnosis, and treatment. The wealth of information and the length of the paper preclude abstraction. It is pertinent and timely, in view of the current articles attributing various ocular and neurological manifestations to temporal-lobe herniation secondary to brain swelling.

NYSTAGMUS

Examination and Interpretation.—The interpretation of nystagmus is often puzzling. To dispel some of this confusion, Rucker [47] offers a simple classification, based on the anatomy, to aid in understanding its clinical forms. The types are arranged according to the portion of the apparatus involved in ocular motions: optic, labyrinthine, muscular, and central, and miscellaneous. The features of nystagmus due to lesions in various portions of these anatomical divisions are described. The clinical applications of these data in the analysis and interpretation of a case of nystagmus are explained. Since every sentence is informative, the original paper should be studied.

Effect on Visual Acuity.—Patients with multiple sclerosis commonly complain of blurring of vision. This is usually attributed to a residual central scotoma in

46. Atkinson, W. J.: Cerebral Swelling: Its Physiology, Pathology, Clinical Symptoms and Signs, Differential Diagnosis and Treatment, Ann. Roy. Coll. Surgeons England **11**:367-394 (Dec.) 1952.

47. Rucker, C. W.: Nystagmus, Tr. Pacific Coast Oto-Ophth. Soc. **33**:29-43, 1952; Am. J. Ophth. **36**:250-258 (Feb.) 1953.

association with temporal pallor of the optic disk. Nathanson, Bergman, and Bender [48] state that this is not always the case and that the visual blurring in multiple sclerosis is due occasionally to oscillopsia, in which objects appear to move in a jerky fashion from side to side or up and down. This phenomenon is due to an acquired horizontal or vertical nystagmus on direct forward gaze (fixation nystagmus). The authors observed that intravenous injection of amobarbital temporarily abolished the nystagmus and the oscillopsia, with improvement in visual acuity. They feel that this test is of value in determining whether the visual blurring is due to involvement of the macular fibers or to nystagmus. They further point out, however, that this nystagmus is usually too fine to be detected without electrical recordings. It would be interesting to know whether the authors were able to detect this fine nystagmus clinically by the method of observing the optic disc movements with the ophthalmoscope—so-called jelly nystagmus.

TRIGEMINAL NERVE

Herpes Zoster Ophthalmicus.—Dolan and Bucy [49] discuss the mechanism of pain in herpes zoster ophthalmicus. In this condition pain is usually present in the acute stage. Curiously, postherpetic neuralgia rarely ensues in patients under 40 years of age, but occurs with increasing frequency in persons above this age and is commonest in elderly arteriosclerotic persons. Treatment of postherpetic neuralgia is unsatisfactory; section of the trigeminal nerve central to the Gasserian ganglion and section of the spinal root of the trigeminal nerve in the medulla oblongata fail to relieve the pain. Although the principal sensory innervation of the face is the trigeminal nerve, the question arises whether other potential sensory pathways from the face (fibers in the sympathetic, vagal, facial, or motor trigeminal system) might be concerned in the production of this pain.

The authors report the case of a man aged 74 with typical trigeminal neuralgia who had a retrogasserian neurotomy of the entire sensory root of the right trigeminal nerve. Freedom from pain, total anesthesia of the right side of the face, and loss of the right corneal reflex resulted and persisted. About one year later severe herpes zoster ophthalmicus developed over the area of distribution of the ophthalmic division of the right trigeminal nerve. He suffered no pain during or subsequent to this acute infection. A similar case was related to Dolan and Bucy in a personal communication from Dr. W. J. Gardner, of Cleveland. From these two cases the authors conclude that (1) herpes zoster ophthalmicus can occur in an area in which the principal sensory innervation has been severed from the central nervous system between the Gasserian ganglion and the brain stem, and (2) the pain of acute herpes zoster ophthalmicus is mediated solely by the trigeminal nerve, and does not occur if the trigeminal nerve has been severed central to the Gasserian ganglion.

Since postherpetic neuralgia does not occur in all persons over 40, one cannot be absolutely certain that postherpetic neuralgia would have developed in either of

48. Nathanson, M.; Bergman, P. S., and Bender, M. B.: Visual Disturbances as the Result of Nystagmus on Direct Forward Gaze: Effect of Amobarbital (Amytal) Sodium, A. M. A. Arch. Neurol. & Psychiat. **69**:427-435 (April) 1953.

49. Dolan, R. A., and Bucy, P. C.: Pain of Herpes Zoster Ophthalmicus, A. M. A. Arch. Neurol. & Psychiat. **68**:314-317 (Sept.) 1952.

these two patients had the trigeminal nerve been intact. It seems likely, however, that only the trigeminal nerve is involved in postherpetic neuralgia. Section of the trigeminal nerve does not relieve postherpetic neuralgia once it has developed. Disease in the peripheral nerve is not the cause of the pain; the nerve serves only as a pathway to the central nervous system, and attention should be centered upon central nervous system mechanisms to explain postherpetic neuralgia.

Raeder's Syndrome.—Bedrossian [50] reports the case of a man aged 59 who had severe pain in the left eye and the left side of the forehead, diminished sensitivity of the left cornea, and Horner's syndrome on the left side, without vasomotor disturbances in the face. Complete recovery followed the extraction of an abscessed left upper lateral incisor tooth. He concludes that the symptoms and signs point to intracranial involvement of the sympathetic fibers, such as is seen in Raeder's syndrome. He does not describe the pathological process by which the abscessed tooth involved the middle cranial fossa.

In my opinion, the combination of involvement of the trigeminal nerve and homolateral sympathetic nerves does not constitute Raeder's syndrome unless the responsible lesion is situated in the middle cranial fossa; in fact, it is the location at this site that led Raeder [51] to employ the term "paratrigeminal" syndrome. The combination of trigeminal and sympathetic nerve involvements does not necessarily indicate that there is an intracranial lesion. Strictly speaking, this case does not appear to be one of a true Raeder paratrigeminal syndrome, and it seems most unlikely that the pathological lesion was located intracranially.

VASCULAR MANIFESTATIONS

The essence of medicine is its ever-changing face. Lesions once common become rare, and rarities become common. This is well exemplified in the increased attention and interest displayed in vascular lesions affecting the brain and eye, and in cerebral angiography, which reveals not only lesions of the vessels themselves but also many space-occupying lesions.

Cerebral Angiography

Perimetry Versus Angiography in Diagnosis.—To evaluate perimetry and angiography in the diagnosis of lesions in the optic chiasmal region, Mooney [52] reported 16 cases of such lesions, including meningioma of the middle fossa, ependymoma, craniopharyngioma, pituitary tumor, meningioma of the tuberculum sellae, mucocele of the sphenoid sinus, internal hydrocephalus due to gliosis of the aqueduct, oligodendroglioma of the frontal lobe, and supraclinoid aneurysm. In each case the diagnoses suggested independently by perimetric studies, x-rays of the skull, and arteriography were compared with the final diagnoses, verified at operation. Mooney states that perimetry still ranks first in localizing value in the investigation of lesions in the chiasmal region. Perimetry generally provides reliable

50. Bedrossian, E. H.: Raeder's Syndrome, A. M. A. Arch. Ophth. **48**:620-623 (Nov.) 1952.

51. Raeder, J. G.: "Paratrigeminal" Paralysis of Oculo-Pupillary Sympathetic, Brain **47**:149-158 (May) 1924.

52. Mooney, A. J.: Perimetry and Angiography in the Diagnosis of Lesions in the Pituitary Region, Tr. Ophth. Soc. U. Kingdom **72**:49-104, 1952.

information concerning the part of the visual pathway affected, the rapidity of growth of the lesion, and the extent of recovery. Angiography is second in importance, as it furnishes confirmatory evidence of the presence of a space-occupying mass, and more complete information concerning the nature of the lesion, the extent to which the tumor has spread beyond the visual pathway, and its suitability for surgical or x-ray therapy. Angiography may demonstrate internal hydrocephalus when other findings suggest intrasellar tumor. The visual field studies, x-rays of the skull, and arteriographic studies are complementary, and this combined information results in earlier and more accurate diagnosis.

It should be noted that the arteriograms revealed a lesion in all 16 of Mooney's cases. It should be emphasized and appreciated, however, that arteriography is not infallible and that a normal or negative arteriogram does not exclude the presence of a mass in the chiasmal region.

Ocular Complications.—Otenasek and Markham [53] report the case of a man aged 51 who manifested recurrent cerebral vascular occlusions. After a right cerebral arteriographic study only large objects could be distinguished with the homolateral eye. Forty-eight hours after three stellate ganglion blocks were done the visual acuity and fields returned to normal. Vasospasm was suggested as the likely mechanism.

Walsh and Smith [54] discuss the ocular symptomatology associated with cerebral angiography. Transient homolateral pain, pupillary disturbances, and petechial hemorrhages in the skin, conjunctiva, and retina may occur. Transient impairment of vision in the homolateral eye is infrequent; the case reported by Otenasek and Markham [53] is cited. Permanent homolateral blindness is rare. Walsh and Smith present the first case ever reported of transient loss of vision in both eyes during the angiographic procedure. A Negro woman aged 24 had severe headaches, occasional "blackouts," slight weakness of the right arm, 20/20 acuity in each eye, and bilateral low-grade papilledema. Left carotid arteriographic examination was without incident; right carotid arteriographic study with simultaneous digital compression of the left carotid artery was performed. Both posterior cerebral arteries filled. Total bilateral blindness developed within a few seconds. Bilateral stellate ganglion block was done 20 minutes later, and light perception returned. Trephination in the left parietal area was done a few hours later. Twenty-four hours after the onset of blindness, visual function returned in the right homonymous half-fields, and 24 hours later the acuity and fields were normal in both eyes. The final diagnosis was serous meningitis. The authors conclude that the bilateral blindness was due to bilateral homonymous hemianopsia and not to impairment of the blood supply to each retina.

Occlusion of Internal Carotid Artery

Ocular Signs.—Thrombosis of the internal carotid artery can produce contralateral hemiplegia and contralateral hemianesthesia. Walsh and Smith [54] discuss the possible ocular signs. These include pupillary disturbances, ophthalmoplegia, retinal hemorrhages, and visual field defects. Three types of field defects can occur:

53. Otenasek, F. J., and Markham, J.: Transient Loss of Vision Following Cerebral Arteriography, J. Neurosurg. **9**:547-551 (Sept.) 1952.

54. Walsh, F. B., and Smith, G. W.: Ocular Complications of Carotid Angiography: Ocular Signs of Thrombosis of the Internal Carotid Artery, J. Neurosurg. **9**:517-537 (Sept.) 1952.

1. Transient or permanent homolateral blindness, due probably to spasm or thrombosis of the central retinal artery. 2. Contralateral homonymous hemianopsia. An important observation in their five cases was the tendency toward sparing of the superior quadrant of the affected half-fields. On the basis of anatomical studies of the arterial blood supply to the visual pathways, the authors believe that the field defects are due to obstruction principally in the branches of the middle cerebral artery supplying the optic radiation. 3. A combination of the first two types, producing homolateral blindness superimposed upon contralateral homonymous hemianopsia.

Philippides, Montrieul, and Lobstein [55] report the case of a man aged 51 who developed unilateral amaurosis. Some of the retinal arteries were narrowed. The neurological examination was noncontributory, but arteriography revealed thrombosis of the ipsilateral internal carotid artery. Later, the optic disc developed pallor. The amaurosis was apparently due to ischemia of the optic nerve secondary to a reflex vasoconstriction. This case serves to show that one internal carotid artery can be occluded without producing neurological signs, and that occlusion of the internal carotid artery should be suspected and considered by the ophthalmologist in the diagnosis of the cause of unilateral blindness of sudden onset.

Retinal Artery Pressure in Diagnosis.—Thomas and Petrohelos [56] measured the systolic and diastolic pressures in the retinal arteries of each eye of 50 control patients and found no significant inequality between the right and the left eyes. In seven of eight patients with occlusion of one internal carotid artery the retinal artery pressures were definitely lower in the ipsilateral eye. The presence of equal pressures does not exclude obstruction of the carotid artery, but, if other reasons for inequality are eliminated, a unilateral lowering of retinal artery pressures is strongly suggestive of a lesion of the internal carotid artery.

Cranial Arteritis

This condition is also referred to as temporal arteritis and as giant-cell arteritis.

Ocular Manifestations.—Parsons-Smith [57] reviews the literature and reports 15 cases of temporal arteritis in which ocular symptoms occurred. These include papilledema with visual loss (ischemic papillitis), thrombosis of retinal arteries and veins, ophthalmoplegias, and alexia. Many ophthalmologists and neurologists are apparently not acquainted with this group of ocular disorders produced by ischemia, and the article is therefore valuable in emphasizing this important condition.

Acute Ischemia of Optic Disc.—Siegert [58] discusses the symptoms and signs of temporal arteritis and classifies three kinds of ocular signs: (1) occlusion of a

55. Philippides, D.; Montrieul, B., and Lobstein, P. A.: Amaurose et thrombose de la carotide interne, Presse méd. **60**:1446 (Oct. 22) 1952.

56. Thomas, M. H., and Petrohelos, M. A.: Diagnostic Significance of Retinal Artery Pressure in Internal Carotid Involvement: Findings in 8 Cases with Carotid-Artery Lesions Compared to 50 Controls and 210 Cases from the Literature, Am. J. Ophth. **36**:335-346 (March) 1953.

57. Parsons-Smith, G.: Ophthalmic Manifestations of Temporal Arteritis, Brit. J. Ophth. **36**:615-625 (Nov.) 1952.

58. Siegert, P.: Akute Ischämie der Papille bei Arteriitis cranialis (temporalis), Klin. Monatsbl. Augenh. **120**:254-273, 1952.

central vessel, producing retinal ischemia; (2) diffuse changes in the retinal vascular system, and (3) acute ischemia of the optic disc. In two cases of acute ischemia the discs were swollen, edematous, and pale; the visual impairment was of sudden onset, severe, and permanent. He believes that this appearance of the fundus is due to pathological changes in the vessels of the intrascleral portion of the optic nerve and that it occurs only in cranial arteritis, although ischemia of the disc may occur without other evidences of cranial arteritis or head signs.

Carotid Artery-Cavernous Sinus Fistula

Lateralization.—Ramos and Mount [59] report an unusual case of a fistula of the right internal carotid artery into the right cavernous sinus, draining through the anterior part of the circular sinus into the left cavernous sinus and left superficial ophthalmic vein. The clinical features of subjective noise in the head, ptosis, ophthalmoplegia, exophthalmos, conjunctival congestion, engorged retinal veins, and bruit were all on the left side. Clinically, the fistula was thought to be on the left side, but arteriograms revealed it to be on the right; apparently, the right ophthalmic veins did not join the cavernous sinus. The diagnostic importance of bilateral carotid arteriography in lateralization is emphasized, although this particular anatomical anomaly is rare.

Glaucoma.—Weekers and Delmarcelle [60] point out that intraocular hypertension is a fairly constant sign in patients with carotid artery-cavernous sinus fistula. They observed glaucoma in five cases; it was homolateral to the fistula in three cases and bilateral in two. With the aid of recent techniques, the authors conclude that the glaucoma is due to increased episcleral venous pressure.

Differential Diagnosis.—Pulsating exophthalmos occurring after a head injury is usually attributed to a carotid artery-cavernous sinus fistula. That this is not necessarily so is demonstrated by Verbiest,[61] who reports two cases of post-traumatic exophthalmos due to a different condition: perforation of the orbital roof, which previously had become thinned and eroded as a result of asymptomatic chronic internal hydrocephalus. Clinically, the involved eye was displaced downward, with impaired elevation; chemosis was present in one case and absent in the other; the pulsations diminished on compression of the internal carotid artery, and no vascular thrills or murmurs could be detected. In both cases, part of the frontal lobe of the brain had herniated into the orbit and was palpable through the upper eyelid as a soft mass above the eyeball. X-ray studies are essential, but the defect in the orbital roof may be evident only in the occipitomental view. Ventriculography reveals the hydrocephalus. Treatment consists, first, of relieving the hydrocephalus, and then reducing or excising the herniated brain, with plastic repair of the defect in the orbital roof.

59. Ramos, M., and Mount, L. A.: Carotid-Cavernous Fistula with Signs on Contralateral Side: Case Report, J. Neurosurg. **10**:178-182 (March) 1953.

60. Weekers, R., and Delmarcelle, Y.: Pathogenesis of Intraocular Hypertension in Cases of Arteriovenous Aneurysm, A. M. A. Arch. Ophth. **48**:338-343 (Sept.) 1952.

61. Verbiest, H.: Post-Traumatic Pulsating Exophthalmos Caused by Perforation of an Eroded Orbital Roof by a Hydrocephalic Brain, J. Neurosurg. **10**:264-271 (May) 1953.

THE HIGHER VISUAL FUNCTIONS

The higher visual functions and perceptual processes are intimately bound up with the higher intellectual processes, but papers dealing with these highly complex and unexplained phases of cerebral physiology and psychology are too detailed and numerous to present in summary form. The following article, however, deserves the attention of ophthalmologists.

Tactile Thought and the Blind.—In a beautifully written paper, Critchley [62] discusses several fascinating neurological aspects of Braille reading. 1. Louis Braille's empirical invention is just within the bounds of normal human tactile discriminative powers. The embossed dots are 3 mm. apart, whereas the threshold of tactile discrimination over the finger tips is 2 mm. Each of the 63 symbols in Braille typology is composed of one or more bosses within a cluster of six possible spaces; the normal limit of the power of discriminating separate contacts at a single, synthetic, immobile contact happens to be six points. 2. The practiced Braillist interprets about 2,000 bosses as he reads about 100 words per minute. The master finger is usually the left forefinger, but may be the right or both forefingers. 3. Several finger tips may simultaneously touch the dots, but the sense data from only the master finger or fingers are regarded by the brain. 4. The physiological mechanism of this acquired process of learning to read Braille is debatable. 5. A skilled Braillist pays no attention to individual dots but identifies each symbol as a whole—a tactile Gestalt. Factors concerning comparative legibility of the various Braille signs are obscure. 6. Sensory perception is largely an appreciation of a change of state. A moving stimulus is more readily appreciated than is a stationary one. The horizontal sweeping finger movements are extremely important in perception. Blind people often appear more mobile and restless than sighted ones, for they are constantly adding to their knowledge of the environment by storing tactile and proprioceptive images. If exaggerated, these movements are known as "blindisms." 7. Braille reading may be very tiring. 8. The hand preferred for palpation has little relation to ordinary cerebral dominance.

Further discussion concerns the nature of imagery in the mind of a congenitally blind person, his conception of the body image, and his notion of surrounding space. Few cases of successful postoperative acquisition of sight by those born blind have been fully studied from a neuropsychological angle. Spatial distortions are considerable; some objects cannot be recognized at first, especially human faces and figures. The early days of this convalescence are uneasy and exhausting. With the acquisition of a new weapon of experience, the older tools seem to become blunted; acuity of hearing and manual dexterity deteriorate remarkably. The promise of the gift of vision is not altogether a pleasurable one, and is often evaded or resisted. Diderot spoke of one congenitally blind man who said he would prefer God to furnish him with especially elongated arms rather than functioning eyes.

The neurology of the blind is an unexplored field. Problems of spatial orientation and of the mechanism of learning could be studied with exciting interest in those born blind; in patients acquiring blindness at a later age; in congenitally blind persons who have regained sight through surgery; in blind-deaf-mute patients; in blind adults in whom focal diseases of the brain, especially of the parietal lobe, have

62. Critchley, M.: Tactile Thought, with Special Reference to the Blind, Brain **76**:19-35 (March) 1953.

developed, in blind persons in whom aphasia, apraxia, or agnosia has developed, and in persons who through cerebral disease or injury have lost acquired tactile accomplishments.

SYNDROMES

Familial Dysautonomia.—Familial autonomic dysfunction is an important syndrome, championed by Riley,[63] manifesting disturbances in the functions of the autonomic nervous system. Only 33 cases have been gathered, but more will undoubtedly be reported as physicians become acquainted with its clinical features. One hundred per cent of the cases are characterized by defective lacrimation, relative indifference to pain, Jewish extraction, excessive perspiration, drooling, emotional instability, and motor incoordination. Hyporeflexia and skin blotching were found in 97% of cases. Intermittent hypertension occurred in 85% of the cases and prompted surgical exploration for pheochromocytoma in five cases. Less frequent but relevant features are frequent pulmonary infection, breath-holding spells in infancy, transient unexplained fever, urinary frequency, cyclic vomiting, convulsions, and corneal ulceration. Mental retardation had been regarded as a regular feature in an earlier report,[64] but a study of later cases revealed that some children show actually superior intellectual endowment. The pathogenesis is unknown.

Ophthalmologists should be alert to this syndrome, because the common presenting complaint of the parents is failure of the child to produce tears in normal fashion when crying. The eyes are not dry, and tear production seems adequate to maintain corneal health; but occasionally after slight trauma or no known trauma an area of haze develops in the cornea, which stains with fluorescein, and ulceration ensues.

From personal experiences with a few patients with this condition, I have been impressed with the unusual behavior of the corneal involvement. The bulbar conjunctiva remains white; even though the corneal ulceration is marked, there is usually not the slightest conjunctival hyperemia. Furthermore, the child does not complain of pain, and there is no blepharospasm. The cornea, with or without ulceration, is hypesthetic or anesthetic. The absence of subjective discomfort and the lack of objective signs serving to attract the attention of the parents permit the ulceration to advance until finally the parents notice the corneal opacity. Treatment is difficult. Closure of the eye with a firm bandage is desirable, but the child usually opens the eye unknowingly under the bandage, thus favoring further trauma to the cornea. Intermarginal lid adhesions may be required. Artificial tears, administered especially at bedtime, often prevent recurrence of the corneal lesions.

Riley emphasized the relative indifference to pain exhibited by these children. They are usually unaware of minor pain and bruises; one child had a broken arm, detected only by the appearance of swelling. Irrigation of the conjunctival sac and removal of adhesive tape from the face elicit no complaint.

Pheochromocytoma and the Phakomatoses.—The four related neurocutaneous syndromes, or phakomatoses, are multiple neurofibromatosis (von Recklinghausen's

63. Riley, C. M.: Familial Autonomic Dysfunction, J. A. M. A. **149**:1532-1535 (Aug. 23) 1952.

64. Riley, C. M.; Day, R. L.; Greeley, D. M., and Langford, W. S.: Central Autonomic Dysfunction with Defective Lacrimation: Report of 5 Cases, Pediatrics **3**:468-478 (April) 1949.

disease), angiomatosis of the retina and cerebellum (von Hippel-Lindau disease), tuberous sclerosis (Bourneville's disease), and encephalotrigeminal angiomatosis (Sturge-Weber disease). In these conditions a disorder of the central nervous system is suspected from finding an abnormality in the skin or the ocular fundus.

It has been known for some time that at least 10% of the cases of pheochromocytoma are associated with multiple neurofibromatosis. In a significant report, Glushien, Mansuy, and Littman[65] describe two cases of pheochromocytoma associated with angiomatosis of the retina (von Hippel disease). These are apparently the first two cases reported in which the two conditions have actually been observed. In recent reviews of the ocular manifestations of pheochromocytoma no mention was made of angiomatosis of the retina. In addition to the known relationship between pheochromocytoma and neurofibromatosis, the authors believe that there is also a relationship between pheochromocytoma and von Hippel-Lindau disease. To date, no case reports have linked tuberous sclerosis or encephalotrigeminal angiomatosis with pheochromocytoma, but the authors anticipate this possibility.

Patients with a neurocutaneous disease should be suspected of having pheochromocytoma, especially if hypertension is present. Conversely, patients with pheochromocytoma should be examined carefully for evidence of one of the neurocutaneous syndromes. The prognosis in pheochromocytoma is probably poorer if the disease is associated with one of the phakomatoses.

In angiomatosis of the retina there develops, usually in the periphery of the retina, a small spherical tumor fed by a pair of large tortuous vessels extending from the disc. Fullness of the retinal veins may be one of the earliest signs. Edema, hemorrhages, and exudates may develop about the tumor mass and in other parts of the retina, especially in the macular area; these may overshadow the vascular tumor. Papilledema may accompany or precede the peripheral retinal changes. It is apparent that an examiner unfamiliar with the appearance of retinal angiomatosis or lacking the knowledge that it may occur in a patient with pheochromocytoma may mistake the fundus changes for evidence of hypertensive retinopathy.

65. Glushien, A. S.; Mansuy, M. M., and Littman, D. S.: Pheochromocytoma: Its Relationship to the Neurocutaneous Syndromes, Am. J. Med. **14**:318-327 (March) 1953.

News and Comment

GENERAL NEWS

Postgraduate Course in Ophthalmology, State University of New York at Syracuse, Medical Center.—The Department of Ophthalmology of the State University of New York at Syracuse, Medical Center, will present its fourth annual postgraduate course in ophthalmology at the Hotel Syracuse, Friday and Saturday, December 11 and 12, 1953.

The following guest lecturers will participate: Dr. Alan C. Woods, Dr. Harold Falls, Dr. Hunter H. Romaine, and Dr. Franklin M. Foote.

The tuition fee will be $25, payable to the State University of New York at Syracuse, Medical Center, Irving Ave., Syracuse, N. Y. This fee covers tuition, daily luncheons, and dinner on Friday night. The course will be limited to 60 members. These will be accepted in the order in which applications, accompanied by checks, are received. Inquiries regarding the course may be addressed to Harold H. Joy, M.D., 504 State Tower Bldg., Syracuse, N. Y.

International Symposium on General Physiology and Pathology of the Eye.—After the International Congress of Ophthalmology and the meeting of the American Academy of Ophthalmology and Otolaryngology in New York, an International Symposium of the General Physiology and Pathology of the Eye will be held at the Department of Ophthalmology, State University of Iowa College of Medicine, Iowa City.

This symposium will be held on Sept. 24 and 25, 1954. The following guest speakers will participate: G. von Bahr (Sweden), G. B. Bietti (Italy), J. Boeck (Austria), H. Henkes (Netherlands), G. B. J. Keiner (Netherlands), H. K. Mueller (Germany), and E. Wolff (England). All papers and discussions will be in English. The detailed program will be announced at a later date.

International Organization Against Trachoma.—A meeting of the Council was held on the forenoon of June 22, 1953, at Maison de Chimie, Rue St. Dominique, Paris.

Reference was made to the report on the treatment of trachoma by sulfonamides and antibiotics recommended by a committee nominated by the World Health Organization, Geneva. Four members of the Council, International Organization Against Trachoma, took part, Prof. Bietti (Italy), Dr. Pagès (Morocco), Dr. Nataf (Tunisia), and Dr. Maxwell Lyons (United Kingdom). The report was published in *Internationale du trachome* (The International Review of Trachoma), No. 4, 1952.

Dr. P. Bailliart (France) and Prof. G. B. Bietti (Italy) were elected to the newly created posts of vice-presidents. Prof. Arnold Sorsby (Great Britain) was elected secretary-general in place of Prof. Mulock Houwer, resigned. The following were elected as additional members of the Council: Dr. Maxwell Lyons, of the World Health Organization, Geneva; Dr. Phillips Thygeson, (United States), and Dr. Busacca (Brazil).

In the afternoon a scientific meeting was held in conjunction with La Ligue Contre le Trachome, at which discussions on various aspects of trachoma took place.

University of Florida Midwinter Seminar in Ophthalmology and Otolaryngology.—The eighth annual midwinter seminar will be held in January, 1954, convening Jan. 18 and continuing through Jan. 23. As in previous years, Miami Beach will be host city.

The lectures on ophthalmology will be presented on Jan. 18, 19, and 20. The lecturers for the courses in ophthalmology will include such distinguished teachers as Dr. W. B. Anderson, Durham, N. C., Dr. W. P. Beetham, Boston; Dr. W. C. Owens, Baltimore; Dr. A. B. Reese, New York, and Dr. M. C. Wheeler, New York.

The complete program, with a schedule of the lectures and the titles of all papers, will be announced later.

Dr. Sanford R. Gifford to Be Honored.—Dr. Sanford R. Gifford is to be honored as a former member of Passavant Memorial Hospital's medical staff who made distinguished contributions to medicine while practicing, teaching, and conducting research at the Hospital, it is announced today.

A commemorative unit dedicated to Dr. Gifford will be part of the new ten-story South Pavilion addition to the hospital, for which funds are currently being raised.

Mr. Eugene Holland is serving as chairman of the Sanford R. Gifford Commemorative Fund. The financing of the various commemorative units among the friends and colleagues of the doctors to be honored will be coordinated with the Building Fund, under the direction of Gilbert H. Scribner Jr.

Dr. Gifford was professor of ophthalmology at Northwestern University Medical School and chairman of the department of ophthalmology. He was also head of the department at Passavant Hospital. He held many offices in professional organizations, including that of president of the Chicago Ophthalmological Society and first vice-president of the American Academy of Ophthalmology and Otolaryngology. His two textbooks, "Ocular Therapeutics" and "Textbook of Ophthalmology," are widely used. He was awarded, posthumously, the Howe Medal for research in ophthalmology.

Passavant Hospital was founded in 1865. It is affiliated with Northwestern University Medical School in a continuous program of teaching and research. Every member of its staff is also a member of the Medical School faculty.

The new building will provide the hospital with 100 more beds, as well as with more teaching beds. It will also provide greatly improved facilities, teaching, and laboratory space, with specialized areas for various departments.

The cost of the new South Pavilion, including extensive remodeling within the hospital, will be $3,000,000. More than half the amount needed has already been subscribed by individuals, firms, and foundations.

PERSONAL NEWS

Dr. Thomas R. Gaines President-Elect of South Carolina Medical Association.—Dr. Thomas R. Gaines, ophthalmologist of Anderson, S. C., has been elected president of the South Carolina Medical Association for the coming year.

SOCIETY NEWS

Société Française ophtalmologie.—The 60th meeting of the Société Française de ophtalmologie was held in Paris June 21 through June 25, 1953. As usual, a great number of foreign members attended (the French Society has as many foreign as French members). Most of these came from European countries, namely, England, Belgium, Switzerland, and Italy; but the Western Hemiphere was well represented, with Conrad Berens, Algernon Reese, and Ramon Castroviejo from New York, I. S. Tassman from Philadelphia, Pacheco Luna from Guatemala, Jorge Malbrán from Argentina, and Moacyr Alvaro, Hilton Rocha, and Moura Brazil from Brazil.

Every year the French Society publishes a book ("Rapport"), which is sent free to its members a month or so before the meeting and is discussed on Tuesday. (The volume can be purchased by nonmembers by applying to the treasurer of the Society, Dr. Jean Charpentier, 28 rue Vignon, Paris, or to the publisher, Masson & Cie, 120 Boulevard Saint-Germain, Paris 6e, Price, 3,300 francs.) This year the volume was

devoted to gliomas and pseudogliomas and had been written by Dr. M. A. Dollfus and Dr. B. Auvert. It has 525 pages and 120 figures. The first part, on gliomas, had an extensive chapter on genetics and dealt thoroughly with the treatment of the second eye in bilateral cases: diathermy, x-ray therapy, and radium therapy. In the second part, on pseudogliomas, the main interest was in the study of retrolental fibroplasia. There is no certainty as to the cause of this disease, but there is a strong suspicion that lack of oxygen may be a factor. There followed an interesting discussion, in which a dozen members took part.

On Monday, June 22, the papers were on the conjunctiva and the sclera. Thomas, Cordier, and Algan (Nancy) read a paper on conjunctival lesions due to Pasteurel la septica. Toulant and Larmande (Algiers) stated that conjunctivitis due to Week's bacillus was particularly frequent and severe in hot climates; 60% of cases of blindness in North Africa were due to it. Moacyr Alvaro (São Paulo) has had excellent results during the last 15 years by treating pterygium with beta rays and surgery combined. Jonquères and Gaillard (Paris) read a paper on transplantation in diseases of the conjunctiva. The material used varied according to the disease: autograft, grafts taken from a cadaver, or grafts from the mouth, amniotic membrane, or skin. Beauvieux and Pesme (Bordeaux) reported a case of symmetrical lipoma of the conjunctiva. Nataf and Delon (Tunis) have for some years been studying the conjunctival lymph channels after selective coloring. This is their second paper. Renard, Lelièvre, and Mazel (Paris) reported on grafts in the treatment of sclero-malacia. They experimented with several materials. Fritz (Brussels) has used a new instrument to measure the pressure in aqueous veins and episcleral blood vessels.

On Wednesday, June 24, papers were on the cornea. Viallefont, Paycha, and Boudet (Montpellier) reported on an investigation of the pathogens of posterior keratitis. Palazon (Murcia) advocated a new instrument to help in centering accurately the corneal transplants. Jarry and Loisillier (Paris) have experimented with cortisone in treatment of corneal wounds in rabbits. Sédan (Marseilles) stressed the frequency of corneal hypesthesia in vernal conjunctivitis. Hervouet and Lenoir (Nantes) read a paper on ocular aspergillosis. Busacca (São Paulo) read a paper on posterior detachment of the vitreous. François, Rabaey, and Vandermeerssche (Ghent) studied the corneal stroma with the electronic microscope. Dejean (Montpellier) studied experimental tuberculosis in the rabbit when inoculated with a limited number of bacilli: the choroidal lesions were very like those observed in man, but secondary corneoscleral lesions were very malignant. Offret and Saraux (Paris) stressed the importance of puncture of the anterior chamber and study of the aqueous in cases of keratitis and uveitis. Paufique (Lyon) has had good results in Fuchs's corneal dystrophy. He peels off, with a curette, the endothelium and Descemet's membrane; a few months later a penetrating transplantation is performed.

On Monday 22 and Thursday 25 "free" papers were read; i. e., the papers could be on any subject. Druault-Toufesco (Tours) considered that the etiology of sympathetic uveitis was very probably allergic. Law (London) had studied the correlation between facial asymmetry and ametropia, anisometropia, heterophoria, and strabismus. Valière-Vialeix and Robin (Limoges) had good results with the lacrodacryostomy of Zarzycki in cases of canalicular stricture. Sabbadini (Milan) advised diathermy as a preventive treatment of retinal detachment in cases of retinal tear or when there are degenerated areas of the retina. Dubois-Poulsen and Magis (Paris) found that field defects, which are usually considered as belonging only to glaucoma, such as Bjerrum's scotoma and the "nasal" step, can be met with in various other diseases (choroiditis, retinopathy, optic neuritis, chiasmatic lesions, etc.). Hoffmann and Kluyskens (Ghent) read a paper on angiography in the several types of suprasellar tumors. Bregeat, Fischgold, and David (Paris) studied the changes in the anterior clinoid process when there is a tumor or a vascular anomaly. Desvignes (Paris) read a paper on the pseudopapilledema sometimes observed in normal people. Tassman (Philadelphia) spoke on diabetic retinopathy and illustrated his

paper with fine photographs of the fundus. He stressed the vascular disturbances in the retina and the kidney and discussed the treatment. Legrand (Nantes) gave his statistics on the end-results of glaucoma operations. A good filtration is no guarantee that vision and fields will not continue to deteriorate. Opacification of the lens also darkens the prognosis. Hartmann, Topalis, and Lombard (Paris) have had excellent results with hyaluronidase both in ocular anesthesia and in increasing the penetration of various drugs into the eye. Schiff-Wertheimer, Fortier, and Maria (Paris) reported a case of meningeal reaction secondary to a foreign body of the cornea which was caused by the virus of herpes. Mawas and Herschberg (Paris) had satisfactory results in 9 of 12 patients with Eales's disease treated with testosterone implants. Miller, Sapir, and Levy (Paris) studied the possible correlation of the fundus image and the retinal blood pressure with serum globulin in atheroma and hyperpiesis.

During this five-day meeting there were numerous operative sessions and clinical demonstrations in several Paris hospitals and on Tuesday afternoon a presentation of films. Monday afternoon Dr. Delthil demonstrated the American Optical Company's space-eikonometer in the ophthalmic department of the Lariboisière Hospital.

The usual banquet was on Tuesday evening at the Cercle Interallié, with Dr. Algernon B. Reese presiding. The next day an excursion was organized to the medieval Royaumont Abbey, where a concert was given by the well-known organist André Marchal.

Several other ophthalmological organizations met during the same week: The International Council of Ophthalmology, the League Against Trachoma, and the Entretiens Therapeutiques.

The 61st meeting of the French Society of Ophthalmology will be held in Paris in May, 1954.

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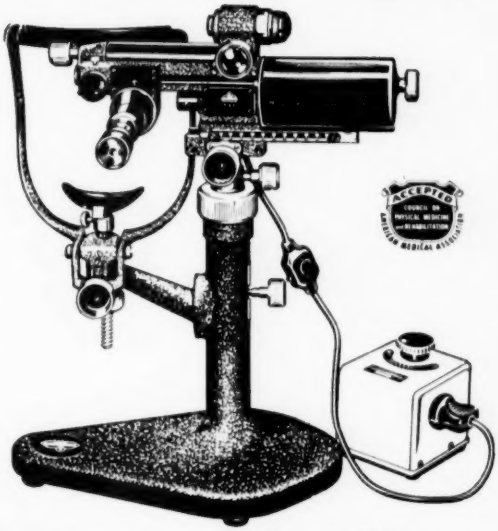

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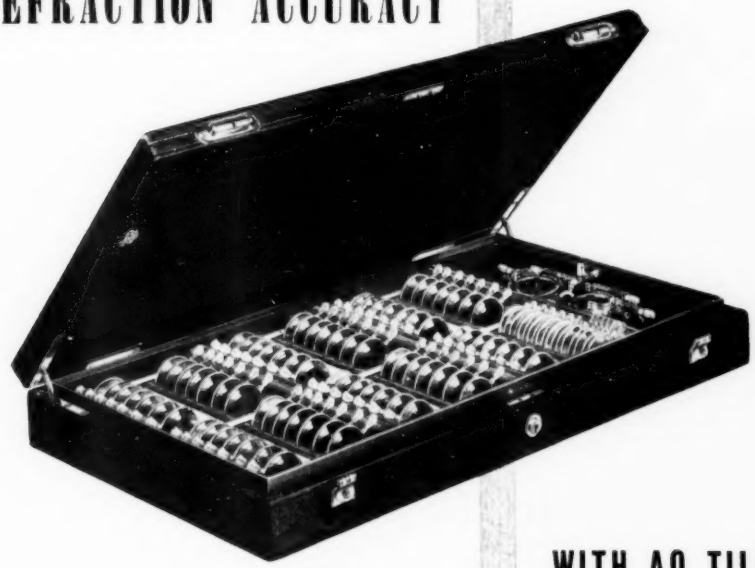

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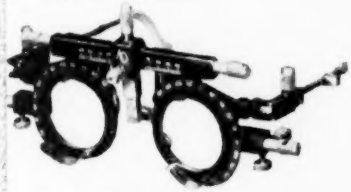

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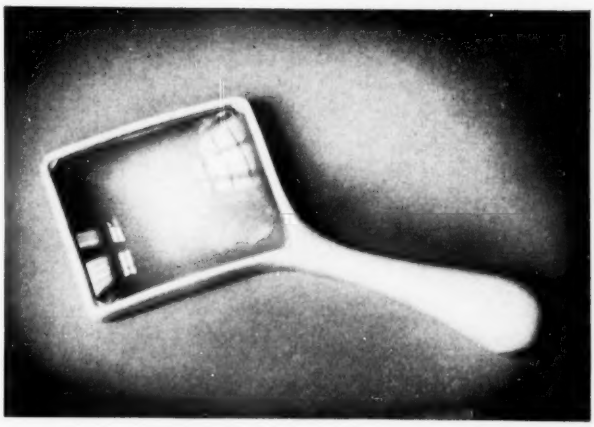

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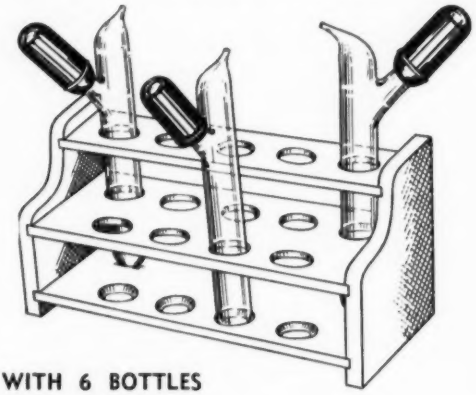

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An electromagnetic detecting device that quickly and accurately locates metallic foreign bodies, including magnetic intraocular foreign bodies. Metallic fragments are readily detected from a satisfactory distance through intervening bone, tissue and fluids. Probing or physical contact with the foreign body is not required for detection.

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Titmus Corrected Curve Lenses are designed to provide clear vision for all object distances over the wide angle field with minimum astigmatic values at the working distance range.

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2. No buffer solutions needed.
3. Fit without a corneal touch.
4. Lens minimally interferes with normal metabolism of the eye. Near normal lacrimal flow and air flow takes place between the lens and the eye when the lens is properly fitted.
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6. No special training is necessary. No special equipment is necessary. No special artistic or mechanical skills necessary. You can fit this lens satisfactorily in your own office without previous contact lens experience. Our consultation service is always open.

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If there is distortion or discoloration of the corneal or scleral section of the eye, then the cosmetic contact lens is made with a clear pupil so that vision is not affected.

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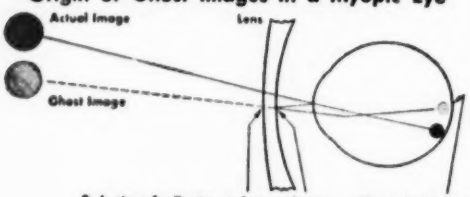
Origin of Ghost Images in a Myopic Eye



Reduction of reflection at these surfaces.....effectively subdues ghost images on retina

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(A. M. A. Standard)

These charts have been prepared in accordance with the compensation tables adopted by the Section on Ophthalmology of the American Medical Association. The set consists of the following:

1—Distance Test Chart (10½" x 28") with notation of acuity and per cent of visual efficiency. (20/20 or 100% to 20/200 or 20%), includes three color bars. **$1.00.**

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(This chart is too large for foreign mailing.)

1—Near Vision Reading Card (5" x 8") with notation of visual acuity and per cent of visual efficiency. (14/14 or 100% to 14/224 or 6.8%.) **40 cents.**

1—Pad of 50 sheets of Industrial Field Charts, printed on both sides. One side of sheet is the Motor Field Chart with table showing efficiency of muscle function in diplopia and gives directions for calculating muscle function. The other side of sheet is the Visual Field Chart showing table, directions and visual field outlines for charting purposes. **75 cents.**

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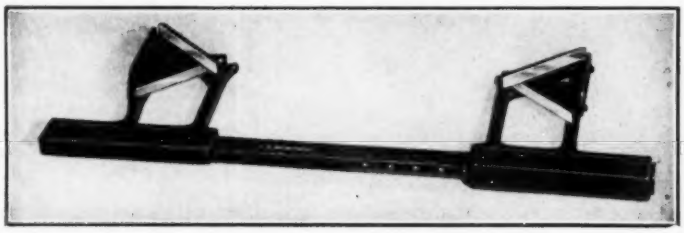
HERTEL EXOPHTHALMOMETER



Improved over the original German model, in that it has front surface mirrors which do away with parallax, this exophthalmometer enables the examiner to measure the degree of exophthalmia accurately and rapidly without assistance.

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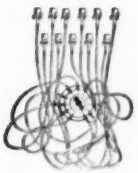

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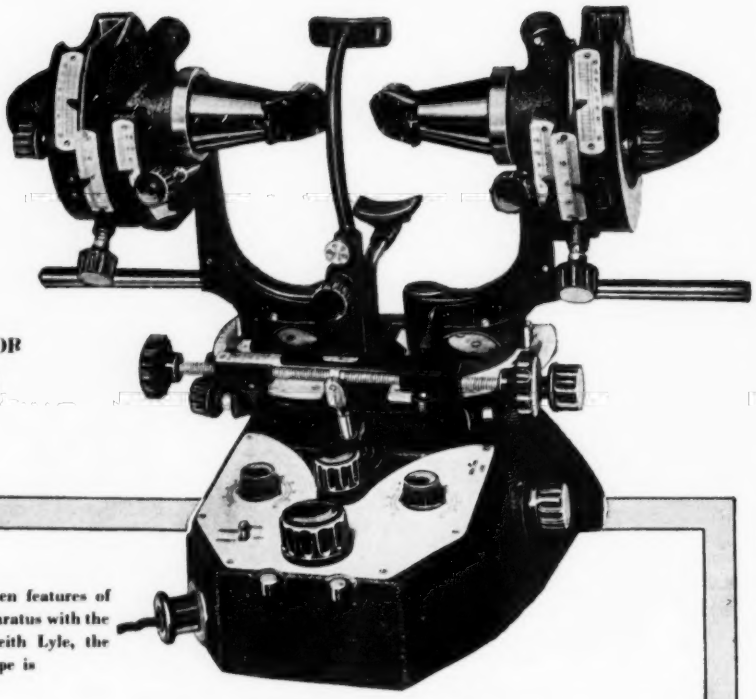

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For rapid relief of congestion, itching, smarting and lacrimation.

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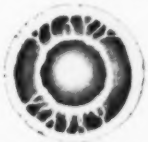
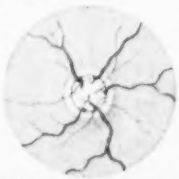
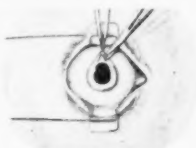


UVEITIS, POSTERIOR SYNECHIAE
10% solution (plain or viscous) or 10% emulsion.
For freeing recently formed posterior synechiae as well as for prevention of synechiae formation in uveitis (with atropine).



GLAUCOMA (certain cases and tests)
10% solution (plain or viscous), 10% emulsion or 2.5% solution.
For temporary reduction of intra-ocular tension and for the provocative test for angle block.



SURGERY
2.5% solution or 10% solution (plain or viscous).
For short acting powerful mydriatic effect, applied 30 to 60 minutes preoperatively.